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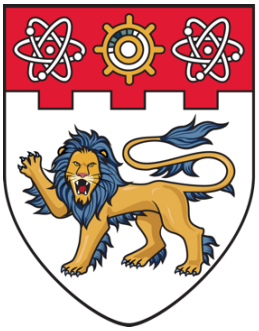
IVAN ŠOLIĆ

2018



NANYANG TECHNOLOGICAL UNIVERSITY
SINGAPORE

# BIMETALLIC, LEWIS ACID AND BRØNSTED ACID CATALYSIS IN ALLYLATION AND OTHER ORGANIC TRANSFORMATIONS

**IVAN ŠOLIĆ**

**SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES**

**2018**

# Bimetallic, Lewis Acid and Brønsted Acid Catalysis in Allylation and Other Organic Transformations

**Ivan Šolić**

**School of Physical and Mathematical Sciences**

A thesis submitted to the Nanyang Technological University
in partial fulfilment of the requirement for the degree of
Doctor of Philosophy

**2018**

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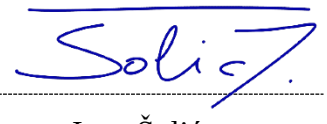

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31 January 2019

Date

Assoc. Prof. Roderick W. Bates

## Authorship Attribution Statement

This thesis contains material from 3 papers published in the following peer-reviewed journals where I was the first author.

Chapter 1 is published as Šolić, I.; Seankongsuk, P.; Loh, J. K.; Vilaivan, T.; Bates, R. W., Scandium as a pre-catalyst for the deoxygenative allylation of benzylic alcohols. *Org. Biomol. Chem.* **2018,** *16* (1), 119-123. DOI: 10.1039/C7OB02219K.

The contributions of co-authors are as follows:

- Assoc. Prof. Roderick W. Bates provided the initial project direction and useful guidance and prepared the manuscript drafts.
- Dr. Tirayut Vilaivan provided useful guidance.
- Dr. Johanna Loh performed initial studies.
- Mr. Pattarakiat Seankongsuk tested additional examples.
- I performed the material synthesis, collected and analysed the data, and prepared supporting information for the published paper.

Chapter 2 is published as Šolić, I.; Lin, H. X.; Bates, R. W., Testing the veracity of claims of Lewis acid catalysis. *Tetrahedron Lett.* **2018,** *59* (50), 4434-4436. DOI: 10.1016/j.tetlet.2018.11.006.

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- Assoc. Prof. Roderick W. Bates provided the initial project direction and useful guidance and prepared the manuscript drafts.
- Mr. Hong Xuan Lin tested several examples in this study.

- I performed the material synthesis for several examples, collected and analysed the data, and prepared supporting information for the published paper.

Chapter 3 is published as Šolić, I.; Reich, D.; Lim, J.; Bates, R. W., Bimetallic Catalysis: Palladium/Lanthanide co-Catalyzed Allylation of Anilines. *Asian J. Org. Chem.* **2017,** *6* (6), 658-661. DOI: 10.1002/ajoc.201600574

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- Assoc. Prof. Roderick W. Bates provided the initial project direction and useful guidance and prepared the manuscript drafts.
- Ms. Jiayan Lim and Mr. Dominik Reich performed initial studies.
- I performed the material synthesis, collected and analysed the data, and prepared supporting information for the published paper.

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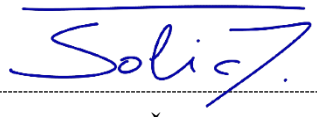

Ivan Šolić

*To my guardian angel…*

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# Summary

The allylic moiety, an important structural motif in organic chemistry, can be easily transformed into many different functionalities. Therefore, it is essential to develop new allylation methodologies.

The first chapter will describe the use of scandium triflate as an efficient catalyst for the deoxygenative allylation of a variety of benzylic and benzyhydryl alcohols. An efficient and robust method for the formation of carbon-carbon bond has been developed. The mechanism of the reaction was studied as well, and it was shown that the reaction actually proceeds through a “hidden Brønsted acid” mechanism.

The second chapter will describe different reactions reported earlier in the literature. It is known that some Lewis acid-catalyzed and Brønsted acid-catalyzed reactions can be ambiguous, selected reactions were hence examined by addition of 2,6-di-*tert*-butyl-4-methylpyridine which is used to reveal the correct reaction pathway.

In the third chapter, different secondary aromatic amines were synthesized and were employed in the bimetallic Pd/La catalyzed Tsuji-Trost type allylation. Underivatized allyl alcohols were used as allylating agents with lanthanum triflate as a water tolerant Lewis acid for hydroxyl activation. The bimetallic Tsuji-Trost type reaction was shown to be an efficient tool for allylation of a variety of nitrogen containing nucleophiles. Thus, it is a good methodology for formation of the carbon-nitrogen bond. Investigation of the scope of the reactivity of nitrogen containing nucleophiles gave both expected and unexpected results. Nucleophiles with good

activating groups have proved to be the best nucleophiles for this bimetallic Tsuji-Trost allylation. Nucleophiles with deactivating groups gave lower yields and require further optimization. Surprisingly, an aminopyridine proved to be an excellent substrate. The reaction also tolerated various substituent groups on the allylic alcohol.

# List of abbreviations

| | |
|---|---|
| Ac | acetyl |
| aq. | aqueous |
| Ar | aryl |
| Bn | benzyl |
| br | broad ($^1$H NMR signal) |
| Bu | butyl |
| n-Bu | n-butyl |
| calcd. | Calculated |
| cat | catalyst |
| Cbz | benzyloxycarbonyl |
| cinn | cinnamyl |
| cod | cyclooctadiene |
| Cp | cyclopentadienyl |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DIAD | diisopropylazodicarboxylate |
| DIBAL-H | diisobutylaluminium hydride |
| DMF | dimethylformamide |
| DMSO | dimethylsulfoxide |
| dt | doublet of triplets |
| DTBMP | 2,6-di-*tert*-butyl-4-methylpyridine |
| EI | electron ionization |
| ESI | electrospray ionization |

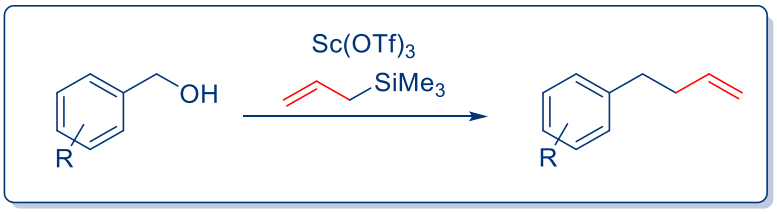
| | |
|---|---|
| Et | ethyl |
| eq. | equivalent |
| h | hour |
| HRMS | high performance liquid chromatography |
| HSAB | hard-soft-acid-base |
| Ln | lanthanides |
| M | molar |
| m | multiplet |
| Me | methyl |
| NMR | nuclear magnetic resonance |
| NOESY | Nuclear Overhauser Effect Spectroscopy |
| Nu | nucleophile |
| OTf | triflate |
| Ph | phenyl |
| PPTS | pyridinium *p*-poluenesulfonate |
| ppm | parts per milion |
| q | quartet |
| r.t. | room temperature |
| RCM | ring closing methatesis |
| s | singlet |
| t | triplet |
| TBS | tert-butyldimethylsilyl |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMS | tetramethylsilane |

| | |
|---|---|
| δ | NMR chemical shift in ppm |
| η | Eta – ligand coordination through multiple atoms |

# Chapter 1

## Scandium triflate as a pre-catalyst for deoxygenative allylation

Scandium triflate has been shown to be an efficient catalyst for the deoxygenative allylation of variety of benzylic and benzyhydryl alcohols, and thus it is a good method for the formation of the carbon-carbon bond.



## 1.1 Introduction

The allylic moiety is a very important structural motif in organic chemistry. Its name comes from the Latin name for garlic - *Allium sativum L.*, due to the plethora of compounds found in it containing the same structural motif (**Figure 1.1**).[1]

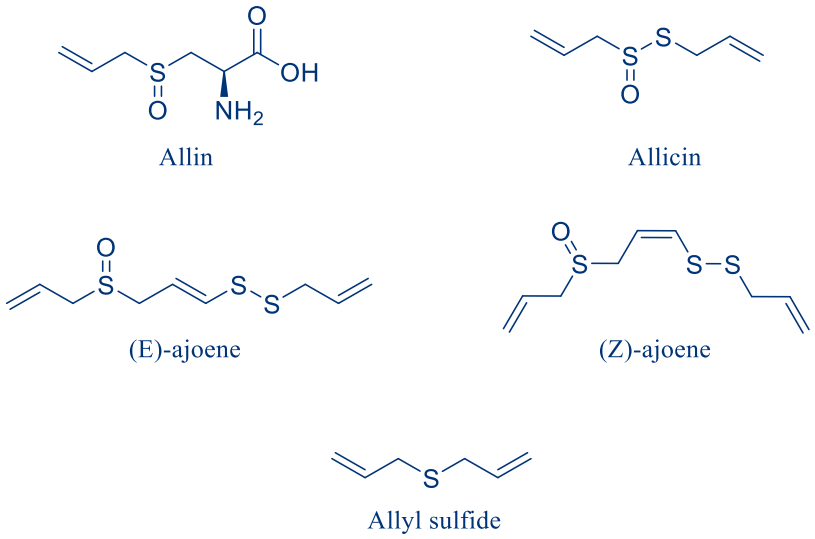
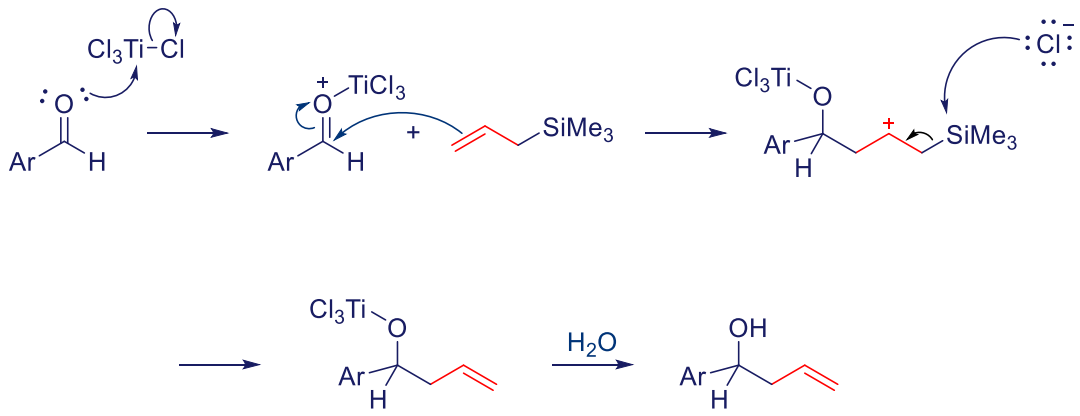



***Figure 1.1.*** *Structures of natural products from garlic (Allium sativum L.) containing allylic moiety*

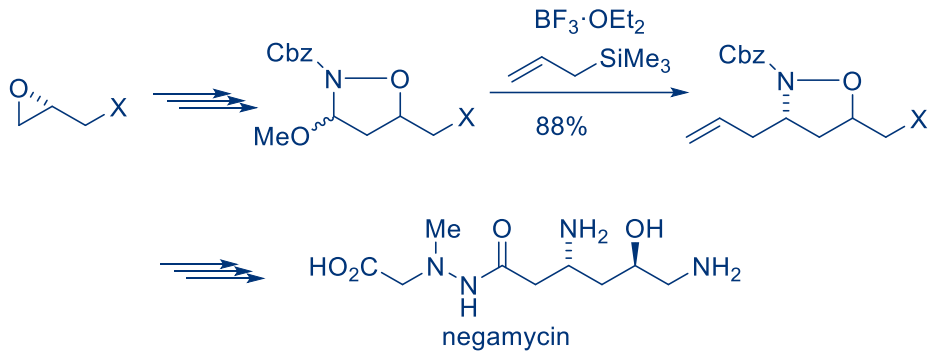
Numerous allylation methods have been reported thus far. One of the important reactions in organic synthesis for carbon-carbon bond formation is the reaction between allyl silane and carbon electrophiles, such as ketones, aldehydes, benzylic alcohols and other related compounds. The resulting compound can be readily transformed into various useful functionalities. Due to the poor reactivity of the allyl silanes towards carbon electrophiles, these reactions usually require some sort of activation in order for the allylation reaction to occur. For example, the Hosomi-Sakurai type reaction requires Lewis acid activation of the carbon electrophile, followed by a nucleophilic attack from the allyl silane.[2-4]




***Scheme 1.1.*** *Mechanism of the Hosomi-Sakurai reaction*

Furthermore, as shown in the mechanism (**Scheme 1.1**), the reaction proceeds through a secondary carbocation intermediate, which is stabilized by the effect of silicon-hyperconjugation (silicon β-effect).

The significance of the Hosomi-Sakurai reaction have been shown in a recent work from our group, where this reaction is one of the key steps in the total synthesis of negamycin (**Scheme 1.2**).[5]




***Scheme 1.2.*** *The Hosomi-Sakurai reaction in the synthesis of negamycin.*

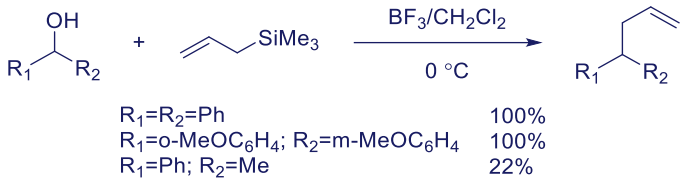
Thus far, it is known that several Lewis acid catalyzed reactions are actually stochiometric, rather than catalytic. This issue generates a large amount of waste which is undesirable in the laboratory and industry. This fact inspires chemists around the world to develop new reactions and methodologies or to improve the old ones.

### *1.1.1 Lewis acid catalysis*

Lewis acids mediated allylation of aldehydes and ketones promoted by allyl silanes has been extensively investigated over the past few decades.[6-8] Additionally, deoxygenative allylation of benzylic alcohols have seen an increasing attention over recent years.

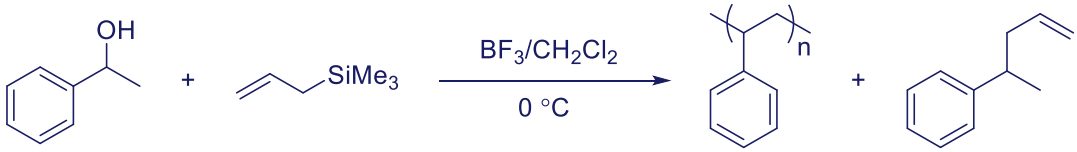
#### *1.1.1.1 Main groups Lewis acids*

Boron species are well known as Lewis acids, and it has been used in one of the first examples of deoxygenative allylation. In 1982 in the work of Cella, boron trifluoride was employed for deoxygenative allylation of arylcarbinols (**Scheme 1.3**).[9]




***Scheme 1.3.*** *Deoxygenative allylation of arylcarbinols by Cella.*

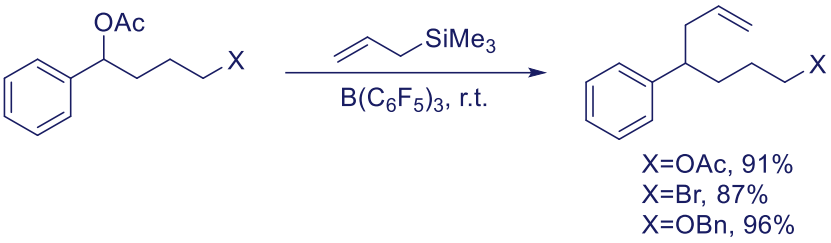
The methodology was efficient for a wide variety of aryl carbinols at 0 °C in dichloromethane. However, simple aliphatic alcohols did not perform as well and undesired polymerization was reported for several examples (**Scheme 1.4**).




***Scheme 1.4.*** *Polymerization as a side reaction in deoxygenative allylation.*

Similarly, in 2001, tris(pentafluorophenyl) borane ($B(C_6F_5)_3$) was used as a catalyst for deoxygenative allylation of secondary aryl acetates with allyl silanes (**Scheme 1.5**).[10] The reaction proceeds smoothly at room temperature to give the corresponding allylated products in high yields. Additionally, the reaction can be used

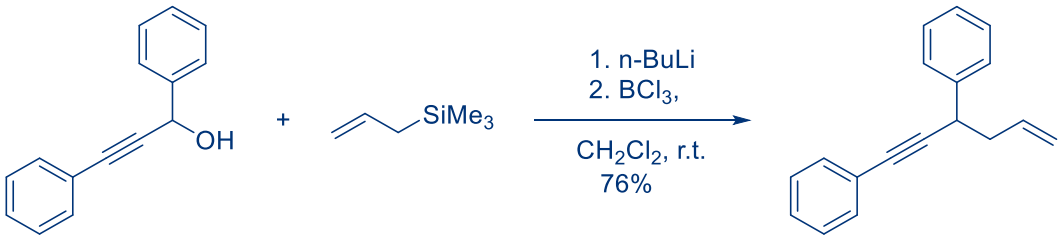
for selective allylation of secondary benzylic acetates in the presence of primary acetates, as expected from the mechanism involving the most stable carbocation.




***Scheme 1.5.*** *Deoxygenative allylation of the secondary acetates.*

Even functional groups such as bromo and benzyloxy-, were tolerated under these reaction conditions.

Recently, Kabalka and coworkers described a method for boron trichloride ($BCl_3$) catalyzed allylation of *in situ* generated lithium propargyl oxides (**Scheme 1.6**).[11]

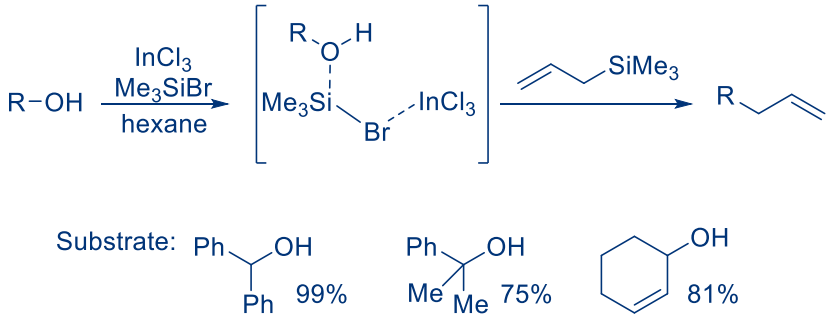



***Scheme 1.6.*** *Deoxygenative allylation by Kabalka et al.*

In the first step, the lithium alkoxide is generated by n-BuLi, followed by $BCl_3$ activation of lithium alkoxide to generate the corresponding cation which subsequently reacts with allyl silane to give the desired product. The above methodology has since been used with a variety of propargylic, benzylic and allylic alcohol substrates.

Another metal from group 13 of the periodic table which acts as a Lewis acid for deoxygenative allylation is indium. There are several reported examples in the literature. For instance, in 2014, Cho's group[12] and Baba's group[13] reported the use of $InBr_3$ and $InCl_3$, respectively. In both cases, indium halides were used on a series of

benzylic alcohol derivatives. Reactions were carried out in dichloromethane at room temperature forming a desired product in good yields. One year later, Baba's group developed an improvement of their method by using an indium-silicon combined Lewis acid catalyst system, more precisely $InCl_3$-$Me_3SiBr$ system.[14] A proposed mechanism for this transformation is shown in **Scheme 1.7**.




***Scheme 1.7.*** *Indium-silicon catalyzed deoxygenative allylation*

Firstly, the bromine from $Me_3SiBr$ coordinates to $InCl_3$ causing an increased Lewis acidity of the silicon center. Subsequently, hydroxyl oxygen coordinates to silicon center, weakening the C-O bond, allowing easier nucleophilic attack by allyltrimethylsilane. Additionally, this method represents a greener version as compared to the previous since the reaction proceeds in a non-chlorinated solvent. A variety of other silyl nucleophiles, such as methallyl-, cinnamyl-, propargyl-, alkynyl-, and allenylmethylsilane can also be applied.[15]

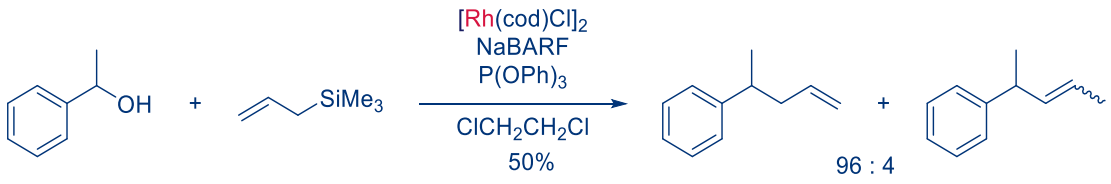
In 2005, the use of bismuth(III) chloride was reported as a Lewis acid for direct deoxygenative allylation of benzylic alcohols and its derivatives.[16] A few years later, $Bi(OTf)_3$ was used for the same transformation,[17] using the ionic liquid, [BMIM][$BF_4$], as a solvent. This catalytic system allows efficient allylation, alkynylation and deoxygenation of alcohols. Additionally, the ionic liquid was successfully recovered and reused.

From the main group elements, molecular iodine represents a special example of a non-metal which shows properties of a mild Lewis acid. In that light, molecular iodine become an interesting Lewis acid in organic chemistry.[18-19] In 2007, the allylation of benzylic acetates and cinnamyl alcohols catalyzed by molecular iodine was reported.[20]

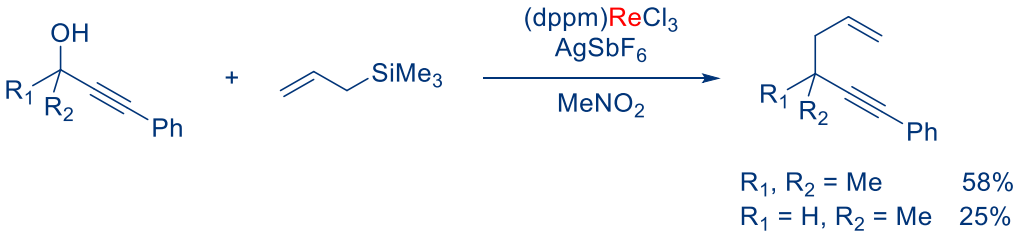
*1.1.1.2 Transition metals Lewis acids*

Titanium tetrachloride is a well-known and a widely used Lewis acid in organic synthesis. An example of $TiCl_4$ catalyzed Hosomi-Sakurai reaction of aldehydes and ketones was presented earlier in the introduction. Likewise, $TiCl_4$ has was also used for deoxygenative allylation of secondary aliphatic and aromatic alcohols.[21]

Moving through early transition metals in the periodic table, other Lewis acids can be found to be employed for this reaction. Examples include $ZrCl_4$,[22] $FeCl_3 \cdot 6H_2O$,[23] $FeCl_3$,[24] or $Fe(OTf)_3$.[25] In the case of late transition metals, several examples have been reported, such as *in situ* generated cationic rhodium (**Scheme 1.8**)[26] or rhenium (**Scheme 1.9**)[27] complexes.

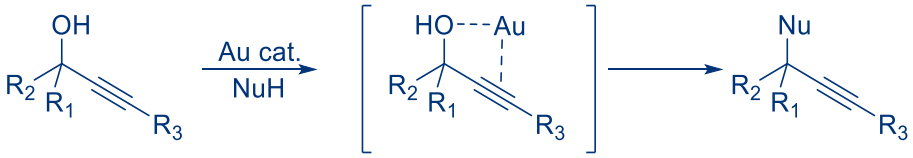



***Scheme 1.8.*** *Rhodium catalyzed deoxygenative allylation of benzylic alcohols*




***Scheme 1.9.*** *Rhenium catalyzed deoxygenative allylation of propargylic alcohols*

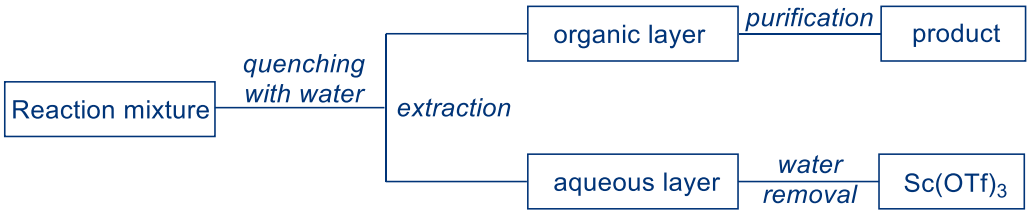
However, in some cases, the use of a late transition metal acts as both a Lewis acid as well as an actual transition metal catalyst. For instance, the use of $NaAuCl_4$ catalyzes the allylation of propargylic alcohols as shown below.[28]




***Scheme 1.10.*** *Gold catalyzed deoxygenative allylation of propargylic alcohols*

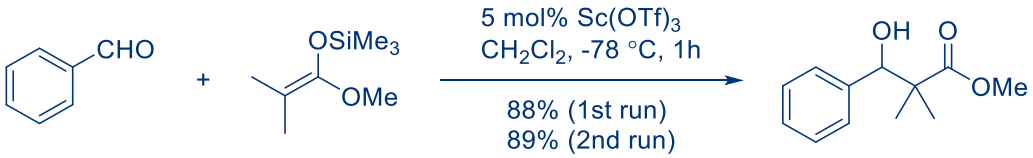
### *1.1.2 Scandium in organic chemistry*

Scandium (Sc) can be found in the periodic table as a member of the 3rd group. It shares the same group with yttrium, lanthanum, and actinium. Due to its chemical properties which are very similar to real lanthanides, scandium is considered as a pseudo-lanthanide.[29] Moreover, both lanthanide triflates ($Ln(OTf)_3$) and scandium triflate ($Sc(OTf)_3$) are advocated to be water stable Lewis acids.[29-31] Furthermore, scandium triflate can also be easily recycled and reused as shown in **Scheme 1.11**.[29]




***Scheme 1.11.*** *Catalyst recovery*

Interestingly, the recycled catalyst performs very well, without any drop in its catalytic activity (**Scheme 1.12**).[32]




***Scheme 1.12.*** *Scandium triflate catalyzed aldol reaction*

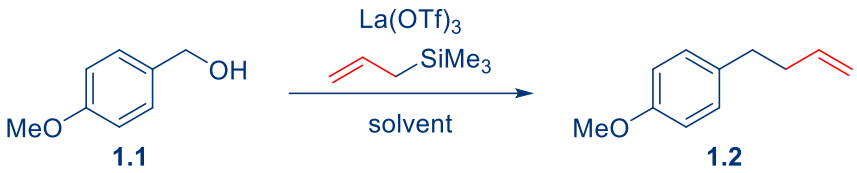
Moreover, the catalytic activity of scandium triflate in several cases is higher than one of lanthanide triflates.[33] In recent years, $Sc(OTf)_3$ has been exploited as a useful catalyst for many organic transformations such as Diels-Alder reaction[31], aldol reaction[34], Mannich-type reactions,[35] Friedel-Crafts acylation,[36] Pechmann condensation.[37] In this chapter, $Sc(OTf)_3$ will be used as a catalyst for deoxygenative allylation of benzylic alcohols and its derivatives.

## 1.2 Results and discussion

### *1.2.1 Initial studies*

Preliminary studies of lanthanide catalyzed deoxygenative allylation were done by Loh, our former group member, using *p*-methoxybenzyl alcohol (**1.1**) as a substrate and lanthanum triflate was chosen as the catalyst. Our intention was to develop a robust synthetic method and, in that light, employing only "bench" solvents, without drying prior to use (**Table 1.1**).

***Table 1.1.*** *Solvent optimization*




**1.1** **1.2**

| Entry | Solvent | Temperature | Yield |
|---|---|---|---|
| 1 | $CH_2Cl_2$ | r.t. | No reaction |
| 2 | EtOAc | r.t. | Trace |
| 3 | 2-Methyltetrahydrofuran | r.t. | No reaction |
| 4 | $CH_3CN$ | r.t. | 6% |
| 5 | $CH_3CN$ | 40 °C | 23% |

Reaction conditions: substrate **1.1** (1 mmol); $La(OTf)_3$ (5 mol%); allyl-TMS (4 eq.); solvent (2 mL).

Initial solvent screening showed poor or no results using dichloromethane, ethyl acetate or 2-methyltetrahydrofuran. Average yields were observed only by using acetonitrile at a slightly elevated temperature (Entry 5).

Subsequently, several lanthanide triflates were tested as a catalyst for this transformation (**Figure 1.2**). Lanthanum triflate, gadolinium triflate, and lutetium triflate were tested, as the elements from the beginning, middle and the end of lanthanide series, as well as scandium triflate which is considered as a pseudo-lanthanide salt.

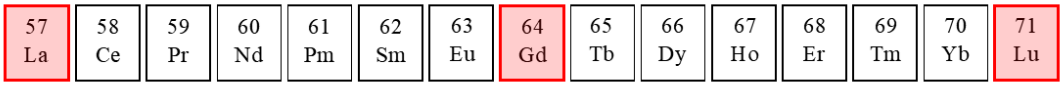
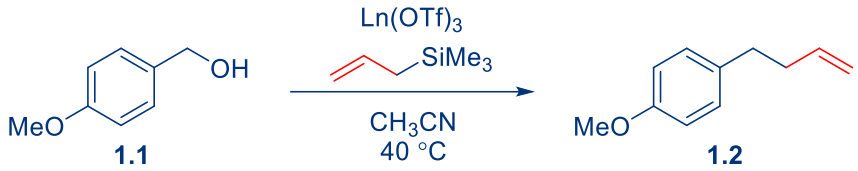



***Figure 1.2.*** *Lanthanides (elements used in this work are highlighted in red).*

Results of the initial catalyst screening are presented in **Table 1.2**. True lanthanum triflate salts (entries 1-3) did not perform well under the given conditions, while scandium triflate showed the best catalytic activity for this reaction.

***Table 1.2.*** *Catalyst screening*




| Entry | $Ln(OTf)_3$ | Time | Yield (%) |
|---|---|---|---|
| 1 | $La(OTf)_3$ | 1 h | 23 |
| 2 | $Gd(OTf)_3$ | 20 h | 15 |
| 3 | $Lu(OTf)_3$ | 20 h | 8 |
| 4 | $Sc(OTf)_3$ | 1 h | 71 |

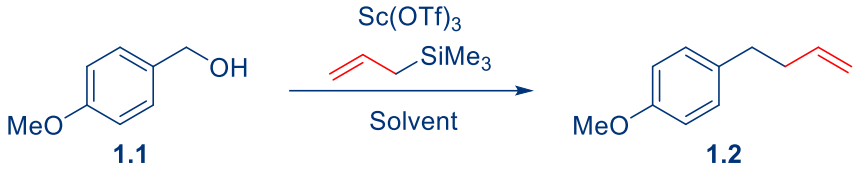
Reaction conditions: substrate **1.1** (1 mmol); $Ln(OTf)_3$ (5 mol%); allyl-TMS (4 eq.); $CH_3CN$ (2 mL).

A slight trend can be observed in the case of entries 1-3. This can be explained by different Lewis acidity of lanthanides which is due to lanthanide contraction. This effect caused by poor shielding of nuclear charge by 4f electrons has a result that lutetium(III) ion is smallest among lanthanides, it has a high positive charge and high Lewis acidity. Due to high Lewis acidity, it strongly attracts triflic anion and thus prevents hydrolysis of $Lu(OTf)_3$ and formation of the free protons in the system which leads to lower yield of this reaction.

With the scandium triflate as a catalyst of our choice, we proceeded to perform additional tests. Since lanthanide triflates have been advocated as water tolerant Lewis

acids,[33] we have decided to test their stability by running the same reaction in the dried acetonitrile and in the acetonitrile mixed with small amounts of water (**Table 1.3**).

***Table 1.3.*** *Reaction performance vs. water content*




**1.1** **1.2**

| Entry | Solvent | Time | Yield (%) |
|---|---|---|---|
| 1 | Dried $CH_3CN$ (45 ppm of $H_2O$) | 1 h | 24 |
| 2 | Bench $CH_3CN$ (130 ppm of $H_2O$) | 1 h | 71 |
| 3* | 2.5% $H_2O$ in $CH_3CN$ | 1 h | Trace |
| 4* | 5% $H_2O$ in $CH_3CN$ | 2 h | - |
| 5* | 10% $H_2O$ in $CH_3CN$ | 2 h | - |
| 6* | 20% $H_2O$ in $CH_3CN$ | 2 h | - |

Reaction conditions: substrate **1.1** (1 mmol); $Sc(OTf)_3$ (5 mol%); allyl-TMS (4 eq.); $CH_3CN$ (2 mL); *solvent system prepared by mixing deionized water with distilled $CH_3CN$.

It was found that the addition of water had a negative effect on the reaction outcome. Only traces of the desired product were observed upon addition of 2.5 % of water (entry 3), while the reaction completely failed when a solvent mixture with higher water concentration was used (entries 4-6). Additionally, using 20% $H_2O$ in $CH_3CN$ (entry 6) as the solvent, two immiscible layers formed. Surprisingly, the reaction was also much less efficient when dried (freshly distilled from calcium hydride) acetonitrile was employed. The exact water content in the solvent and solvent mixtures was determined by Karl Fisher titration.[1] In the distilled acetonitrile was approximately 45 ppm of water, and bench acetonitrile contained around 130 ppm of water. For solvent mixtures with higher water content (entries 3-6), we were unable to

[1] Karl Fisher titration was performed by Gan Sher Li.

determine exact water concentration due to limitations of the instrument. However, this experiment has shown that certain amount of water is required for this reaction. At this stage, we decided to follow Spencer's work, who demonstrated that very often, when Lewis acids are employed, the real catalyst is actually *in situ* generated $H^+$, in other terms a "hidden Brønsted acid".[38] This claim has been tested by adding di-*t*-butyl-4-methylpyridine (DTBMP) as a base in our reaction conditions (**Figure 1.3**).

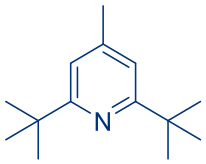
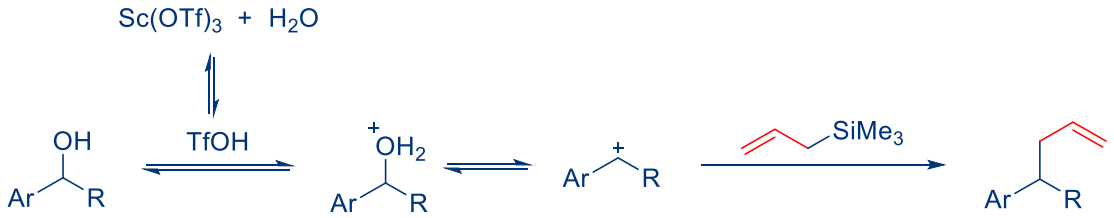



***Figure 1.3.*** *di-t-butyl-4-methylpyridine (DTBMP)*

This pyridine base contains sterically hindered nitrogen which is capable of sequestering a proton but will not coordinate to the Lewis acid.[39] In the presence of this additive, no product was formed. Even at elevated temperatures (90 °C), only 60% conversion was observed after 22 hours. It is thus postulated that this reaction truly proceeds through the hidden Brønsted acid mechanism, which is formed by hydrolysis of the scandium triflate *in situ* as shown in **Scheme 1.13**. Due to the lack of free protons in the system, forcing conditions are required (90 °C).




***Scheme 1.13.*** *The proposed mechanism of the deoxygenative allylation.*

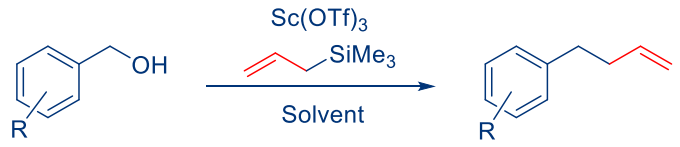
For this reason, scandium triflate should be considered as a pre-catalyst for this reaction. In addition, the reaction was also performed by using scandium acetate. In this case, product formation was not observed, due to the fact that only weak acetic

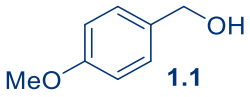
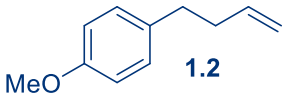
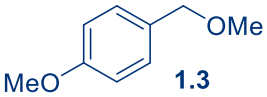
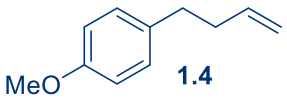
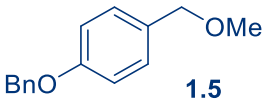
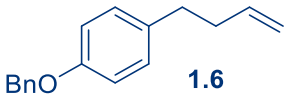
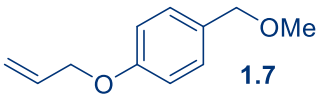
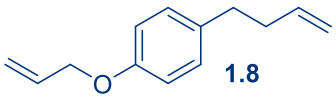
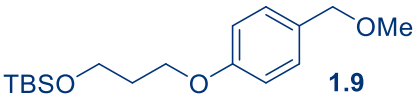
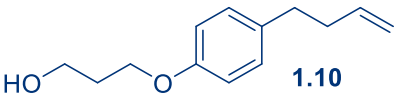
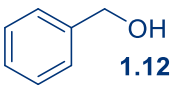
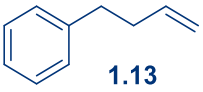
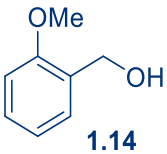
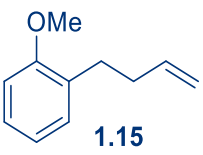
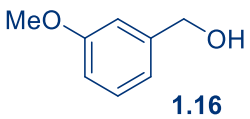
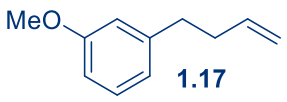
acid is generated by hydrolysis of scandium acetate. Moreover, the reaction can be catalyzed by triflic acid giving 75% conversion in 2 hours. Nonetheless, scandium triflate allows easier handling (thanks to the solid form) and better stability in comparison to triflic acid, which is a very corrosive and easily decomposable liquid.

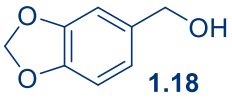
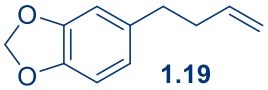
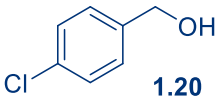
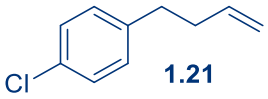
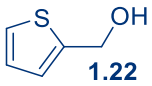
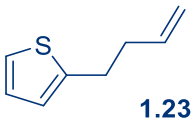
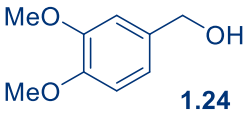
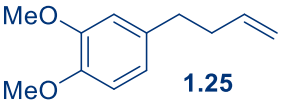
### *1.2.2 Reaction scope*

The substrate scope of was subsequently investigated with a variety of benzyl alcohols and ethers (**Table 1.4**).

***Table 1.4.*** *Substrate scope – benzyl alcohols*

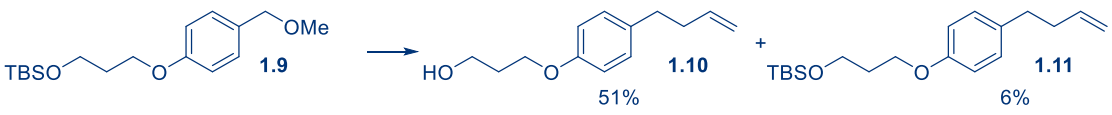



| Entry | Substrate | Product | Yield (%) |
|---|---|---|---|
| 1 |   |   | 71* |
| 2 |   |   | 77* |
| 3 |   |   | 97 |
| 4 |   |   | 94 |
| 5 |   |   | **1.10** 51% **1.11** 6% |
| 6 |   |   | 0* |
| 7 |   |   | 24* |
| 8 |   |   | 0* |

| | | | |
|---|---|---|---|
| 9 |  **1.18** |  **1.19** | 10* |
| 10 |  **1.20** |  **1.21** | 0* |
| 11 |  **1.22** |  **1.23** | trace |
| 12 |  **1.24** |  **1.25** | 15** |

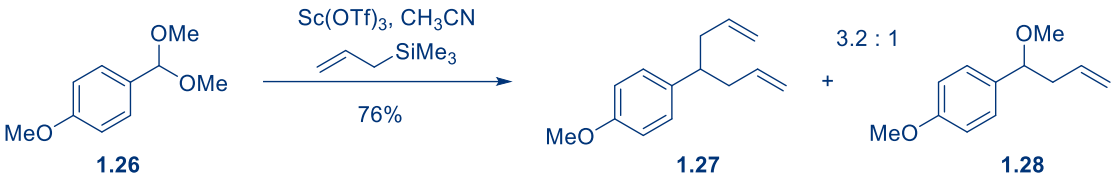
Reaction conditions: substrate (1 mmol); $Sc(OTf)_3$ (5 mol%); allyl-TMS (4 eq.); $CH_3CN$ (2 mL);
* Substrates tested by Loh; ** substrate tested by Seankongsuk

As expected, the corresponding methyl ether performed equally well (entry 2). However, many other benzylic alcohols did not perform well. In the case of benzyl alcohol (entry 6), *m*-methoxybenzyl alcohol (entry 8), and *p*-chlorobenzyl alcohol (entry 10) no product was obtained. Furthermore, low yields were obtained with *o*-methoxybenzyl alcohol (entry 7) and piperonyl alcohol (entry 9). In the above-mentioned cases, low reactivity is expected due to poor stabilization of generated benzylic cation. When *p*-benzyloxybenzyl methyl ether was employed (entry 3), allylation was observed at the more electron rich position. An excellent result was also observed when *p*-allyloxybenzyl methyl ether was employed (entry 4). As expected, TBS protected alcohol substrate (**Table 1.4**, entry 5 and **Scheme 1.14**) yielded a corresponding allylated product with a free alcohol group (**1.10**).[40]



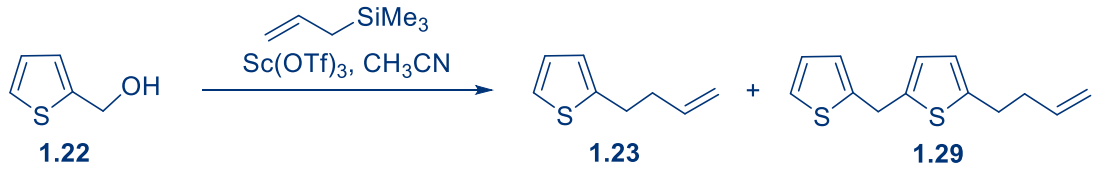

***Scheme 1.14.*** *Deoxygenative allylation of silyl ethers.*

Mono-allylated and di-allylated products were both observed when p-methoxybenzaldehyde dimethyl acetal was employed (**Scheme 1.15**).



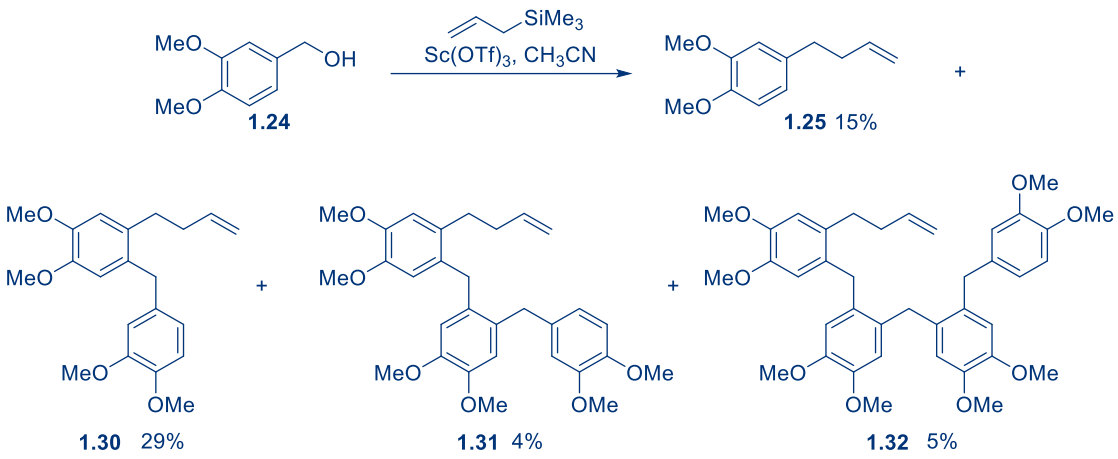

***Scheme 1.15.*** *Deoxygenative allylation of methoxybenzaldehyde dimethyl acetal.*

Low yield of allylation product was observed in the case of thiophenylmethanol (**1.22, Table 1.4**, entry 11), due to the high volatility of the desired compound and oligomerization (**Scheme 1.16**). Similar results were observed previously by several research groups.[9, 17, 41]




***Scheme 1.16.*** *Deoxygenative allylation of thiophenylmethanol.*

Previously our former group member, Seankongsuk, observed similar results when veratryl alcohol (**Table 1.4**, Entry 12, **1.24**) was employed. Veratryl alcohol reacts rapidly, however, the desired allylated product (**1.25**) was observed in very low yield due to oligomerization occurring (entry 12). Along with the desired product, pseudo-dimer (**1.30**), pseudo-trimer (**1.31**) and pseudo-tetramer (**1.32**) were successfully isolated (**Scheme 1.17**). In both cases, aromatic rings of the allylated products are very nucleophilic and due to that, the competing oligomerization reaction occurs competitively.




***Scheme 1.17.*** *Deoxygenative allylation and oligomerization of veratryl alcohol.*

We attempted to solve this problem by using tri-n-butylallylstannane which is four times more reactive nucleophile than trimethylallylsilane.[42] Surprisingly, only starting material was recovered. We suspected that this was due to destruction of Brønsted acid formed in the medium by reaction with stannane. This was confirmed when allyl tri-n-butylstannane was added to scandium triflate in $d_2$-dichloromethane. Bubbles of propene gas could be observed, as well as confirmed by NMR spectroscopy (**Figure 1.4**).[43]

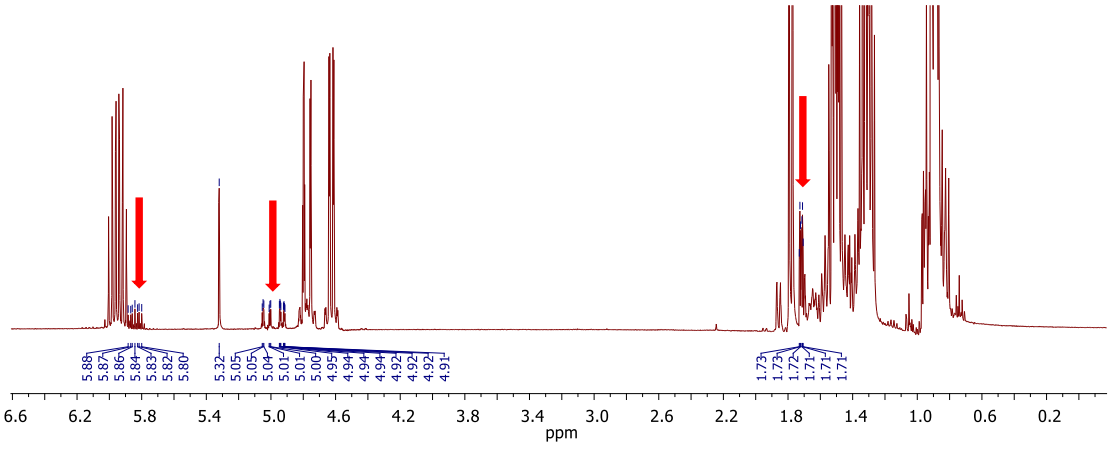
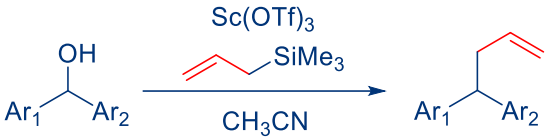


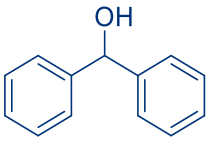
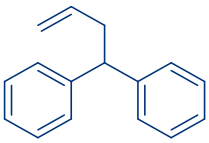
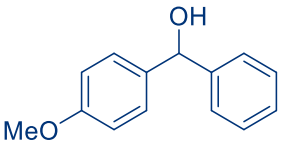
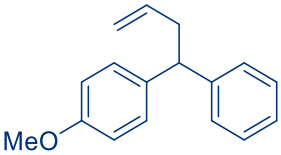
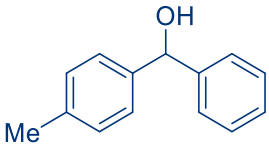
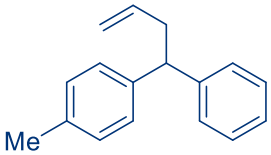
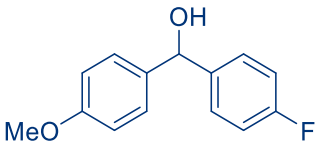
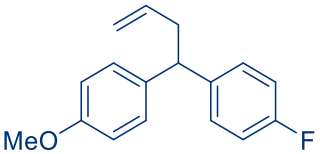
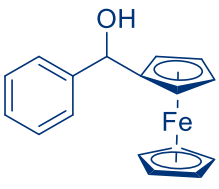
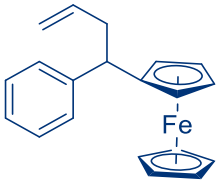

***Figure 1.4.*** *Test reaction (allyl tri-n-butylstannane and scandium triflate in $d_2$-dichloromethane)*

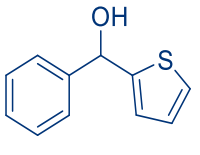
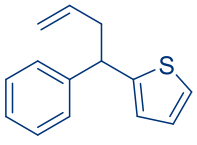
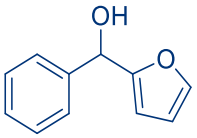
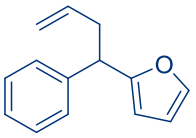
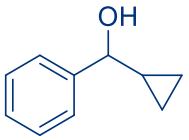
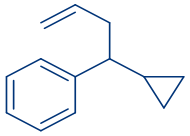
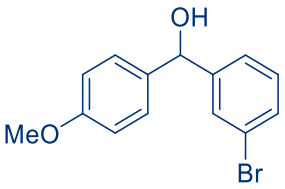
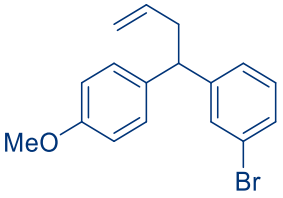
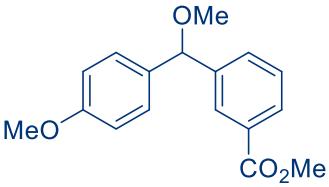
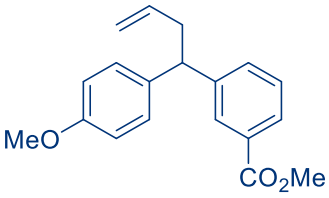
Given that secondary carbocations are more stable than primary, we subjected different benzhydryl alcohols to our reaction conditions (**Table 1.5**). All substrates

were prepared in our group by a Grignard reaction from corresponding aryl aldehyde and aryl halide counterpart, except the ferrocene containing substrate which was prepared by a Friedel-Crafts reaction. The choice of substituents on aromatic rings involves a variety of electron donating and electron accepting groups. This allow us a fine tuning of generated carbocation and thus decent investigation of the reaction scope and investigation of the functional group stability under given reaction conditions.

***Table 1.5.*** *Substrate scope – benzhydryl alcohols*

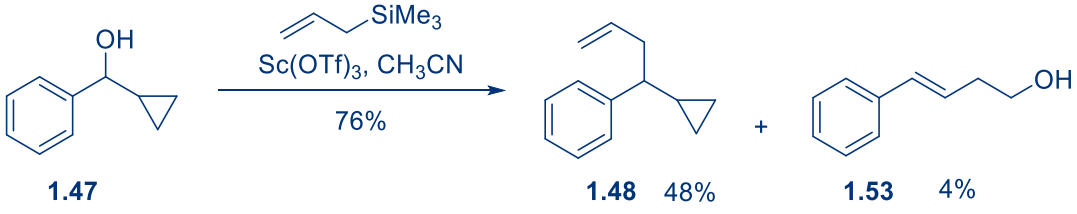



| Entry | Substrate | Product | Yield (%) |
|---|---|---|---|
| 1 |  **1.33** |  **1.34** | 96 |
| 2 |  **1.35** |  **1.36** | 94 |
| 3 |  **1.37** |  **1.38** | 95 |
| 4 |  **1.39** |  **1.40** | 84 |
| 5 |  **1.41** |  **1.42** | 93 |

| | | | |
|---|---|---|---|
| 6 |  **1.43** |  **1.44** | 52 |
| 7 |  **1.45** |  **1.46** | 0 (dec.) |
| 8 |  **1.47** |  **1.48** | 48 |
| 9 |  **1.49** |  **1.50** | 94 |
| 10 |  **1.51** |  **1.52** | 96 |

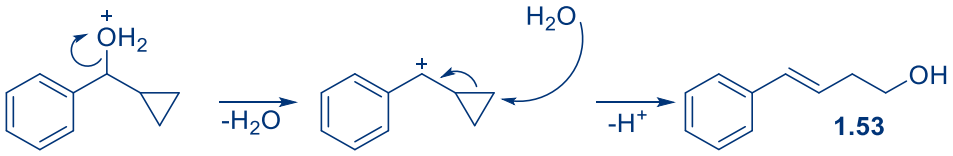
Reaction conditions: substrate (1 mmol); $Sc(OTf)_3$ (5 mol%); allyl-TMS (4 eq.); $CH_3CN$ (2 mL);

Allylation products for this class of compounds were obtained mostly in good yields. One compound that proved problematic was phenyl 2-furyl carbinol (entry 7) as it was very unstable to acidic conditions. The thiophene analog was more stable and the corresponding allylation product was obtained in a better yield (entry 6). In the case of phenyl cyclopropyl carbinol, allylation product was observed in modest yield, accompanied with the ring opening product (**1.53, Table 1.5**, entry 8 and **Scheme 1.18).**




***Scheme 1.18.*** *Deoxygenative allylation of phenyl cyclopropyl carbinol.*

This ring opening product is the Julia product which comes from cyclopropane ring opening caused by the nucleophilic attack of water to the cyclopropyl carbocation intermediate (**Scheme 1.19**),[44] and thus confirms carbocation mechanism.




***Scheme 1.19.*** *Mechanism for the formation of the ring opening product* ***1.53****.*

Lastly, since hidden Brønsted acid mechanism has been confirmed, we have decided to employ a solid supported catalyst. Nafion has been chosen as a perfluorinated sulfonic acid resin (**Figure 1.5**).

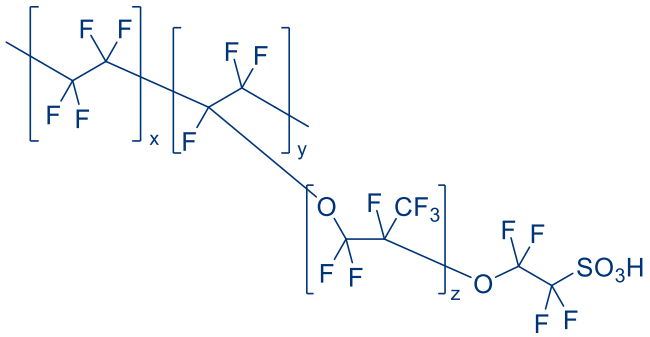
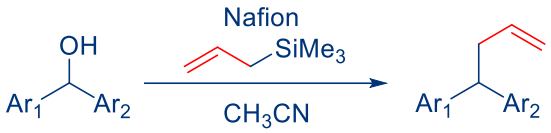
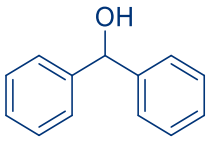
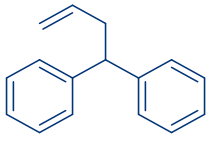
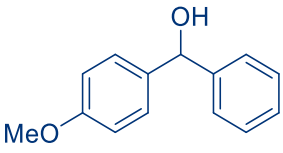
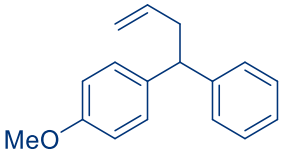
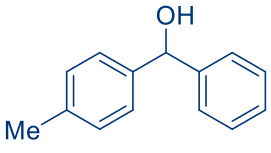
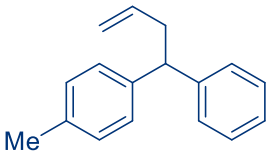
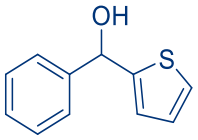
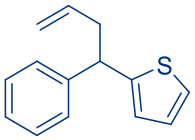



***Figure 1.5.*** *Structure of Nafion*

This modification could potentially simplify the reaction work-up and furthermore could be of use in flow chemistry. Results presented in **Table 1.6**. show modest to good yields for selected substrates.

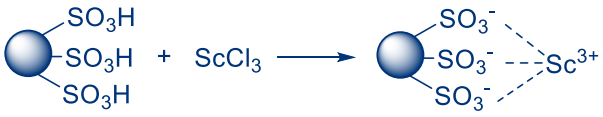
***Table 1.6.*** *Allylation using Nafion*




| Entry | Substrate | Product | Yield (%) |
|---|---|---|---|
| 1 |  **1.33** |  **1.34** | 42 |
| 2 |  **1.35** |  **1.36** | 74 |
| 3 |  **1.37** |  **1.38** | 57 |
| 4 |  **1.43** |  **1.44** | 51 |

Reaction conditions: substrate (1 mmol); Nafion (10 %); allyl-TMS (4 eq.); $CH_3CN$ (2 mL);

Additionally, when Nafion-supported scandium (III) was used (**Scheme 1.20**),[45] no product formation was observed. This result indicates the absence of available protons in this system to promote the reaction and thus confirms the "hidden Brønsted acid" mechanism.




***Scheme 1.20.*** *Preparation of Nafion-supported scandium(III)*

## 1.3 Conclusion

An efficient and robust method has been developed for the deoxygenative allylation of wide variety benzhydryl alcohols. In the case of benzyl alcohols, the reaction shows good results when the generated carbocation is well stabilized. However, the slightly limited substrate scope shows potential useful selectivity.

With various experiments, we have confirmed that the reaction proceeds through a hidden Brønsted acid mechanism. Therefore, scandium triflate is considered as a pre-catalyst in this reaction.

## 1.4 Experimental section

All reactions requiring anhydrous conditions were carried out under nitrogen gas atmosphere using oven-dried glassware. Anhydrous diethyl ether and tetrahydrofuran were distilled from sodium metal and benzophenone. All other solvents and reagents were used as received. The flash column chromatography was carried out on silica gel 230-400 mesh, and analytical TLC on pre-coated glass plates (silica gel 60, $F_{254}$). $^{1}H$ NMR (400 MHz) and $^{13}C$ spectra (100 MHz) were recorded on a JEOL ECA 400 in $CDCl_3$ solutions. Chemical shifts are recorded in ppm and coupling constants are recorded in Hz.

### *1.4.1 Preparation of the benzylic alcohol derivatives*

#### *1.4.1.1 A general method for the $NaBH_4$ reduction (**GP1**)*

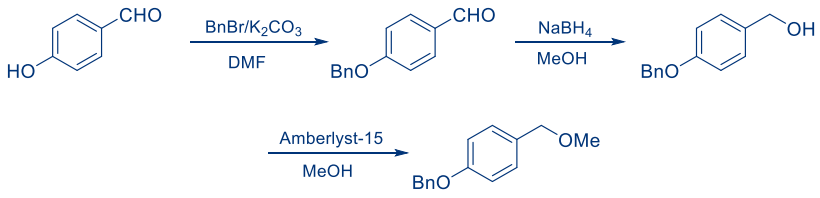
The corresponding carbonyl compound (1 mmol, 1eq.) was dissolved in methanol (5 mL). The reaction mixture was cooled with the ice bath, and sodium borohydride (1 eq.) was added portionwise. The reaction was stirred additional one hour at room temperature and progress was monitored by a TLC analysis. The reaction mixture was quenched with a saturated $NH_4Cl$ solution (2 mL), concentrated under reduced pressure, extracted with ethyl acetate (3 × 5 mL), washed with water (10 mL) and brine (10 mL), and dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. When necessary, the obtained residue was purified by column chromatography.

#### *1.4.1.2 General procedure for the Grignard reaction (**GP2**)*

Magnesium turnings (1.2 eq.) were added into the oven dried, a two-necked round-bottom flask equipped with reflux condenser and rubber septum. Anhydrous $Et_2O$ (5 mL) was added together with one crystal of iodine. The mixture was stirred for 15

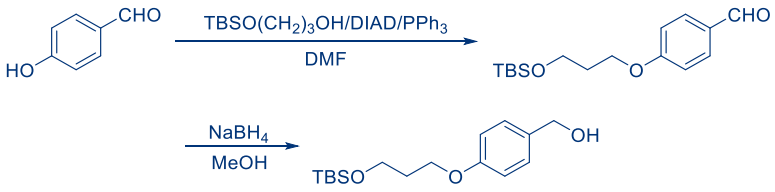
minutes, followed by dropwise addition of corresponding aryl halide (1.2 eq.). The reaction mixture was stirred for additional one hour at room temperature. To the resulting mixture was added corresponding aryl aldehyde (1 eq.) dropwise by syringe. The reaction was monitored by TLC analysis and after completion, the reaction was quenched with $H_2O$ (2 mL) and 2M HCl (2 mL). The aqueous layer was extracted with $Et_2O$ (3 × 5 mL), and the combined organic layer was washed with brine (10 mL) and dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography.

***1-(Benzyloxy)-4-(methoxymethyl)benzene (1.5):***



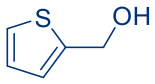

This compound was prepared from 4-hydroxybenzaldehyde according to reported procedure[46], followed by $NaBH_4$ reduction using general procedure GP1, and methylation with Amberlyst-15. The product was obtained as a colorless liquid in 80% yield. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.22 (m, 7H), 6.98 – 6.92 (m, 2H), 5.06 (s, 2H), 4.38 (s, 2H), 3.36 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 158.5, 137.1, 130.7, 129.5, 128.7, 128.1, 127.6, 114.9, 74.5, 70.1, 58.0).

***(4-(3-((tert-Butyldimethylsilyl)oxy)propoxy)phenyl)methanol (1.9):***

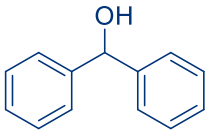



To a solution of 3-((*tert*-butyldimethylsilyl)oxy)propan-1-ol (1.71 g, 9.1 mmol, 1.1

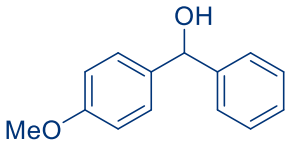
eq.) $PPh_3$ (2.36 g, 9.01 mmol, 1.1 eq) and 4-hydroxybenzaldehyde (1.00 g, 8.2 mmol, 1 eq.) in dry tetrahydrofurane (30 mL) at 0 °C was treated with diisopropyl azodicarboxylate (DIAD) (1.77 mL, 9.1 mmol, 1.1 eq), dropwise. The reaction mixture was stirred at room temperature for 4 hours. The solvent was removed in vacuo, and crude thick yellow oil was purified by column chromatography. Obtained product was reduced with $NaBH_4$ according to general procedure GP1 to give desired product as a yellow oil in 64% yield. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 2H), 6.90 – 6.86 (m, 2H), 4.60 (s, 2H), 4.05 (t, *J* = 6.1 Hz, 2H), 3.79 (t, *J* = 6.1 Hz, 2H), 1.97 (p, *J* = 6.1 Hz, 2H), 0.88 (s, 9H), 0.03 (s, 6H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 158.9, 133.1, 128.8, 114.7, 65.2, 64.7, 59.6, 32.5, 26.1, 18.5, -5.2; **HRMS (EI):** Exact mass calcd for $C_{16}H_{29}O_3Si$ $(M+H)^+$: 297.1886, Found: 297.1890; **MS (ESI):** 297.49 $(M+H)^+$; **IR (NaCl):** 3381, 2951, 2928, 2880, 2855, 1715, 1614, 1514, 1173.



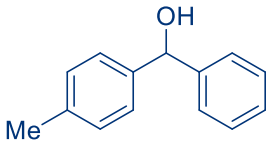

***Thiophen-2-ylmethanol (1.22):*** To a stirred solution of thiophene-2-carboxylic acid (1.50 g, 11.7 mmol, 1 eq.) in anhydrous THF (15 mL), $LiAlH_4$ (2 eq., 0.89 g, 23.4 mmol) was added in a small portion under the seam of nitrogen gas. The reaction mixture was stirred for 30 minutes at room temperature. The reaction mixture was quenched with water, 2 M NaOH, and again with water. After quenching, the reaction mixture was filtered, concentrated under reduced pressure, extracted with DCM and dried over $MgSO_4$. The crude product was purified by column chromatography to give thiophen-2-ylmethanol as a yellow oil. (0.88 g, yield 66%). The obtained NMR data are in agreement with those previously reported in the literature.[47] **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 1H), 7.01 – 6.95 (m, 2H), 4.79 (s, 2H), 2.19 (s, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 144.1, 127.0, 125.7, 125.6, 60.0.



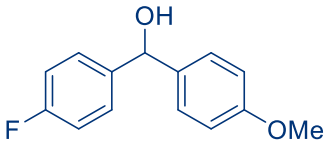

***Diphenylmethanol (1.33):*** This compound was synthesized from benzophenone according to the general procedure **GP1** as a white solid in quantitative yield. The obtained NMR data are in agreement with those previously reported in the literature.[48] **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.13 (m, 10H), 5.84 (d, *J* = 3.5 Hz, 1H), 2.23 (d, *J* = 3.5 Hz, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 143.9, 128.6, 127.71, 126.7, 76.8, 76.4.



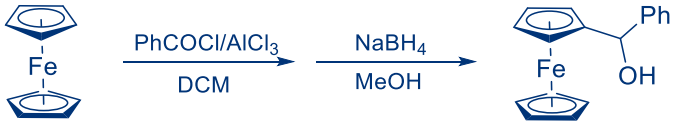

***(4-Methoxyphenyl)(phenyl)methanol (1.35):*** This compound was synthesized from bromobenzene and 4-methoxybenzaldehyde according to the general procedure **GP2** as a white solid in 98% yield. The obtained NMR data are in agreement with those previously reported in the literature.[49] **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.23 (m, 7H), 6.89 – 6.84 (m, 2H), 5.80 (s, 1H), 3.78 (s, 3H), 2.22 (d, *J* = 2.7 Hz, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 159.1, 144.1, 136.3, 128.5, 128.0, 127.5, 126.5, 114.0, 75.9, 55.4.



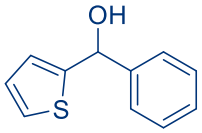

***Phenyl(p-tolyl)methanol (1.37):*** This compound was synthesized from bromobenzene and 4-methylbenzaldehyde according to the general procedure **GP2** as a white solid in 68% yield. The obtained NMR data are in agreement with those previously reported in the literature.[49] **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 4H), 7.27 – 7.23 (m, 3H), 7.14 (d, *J* = 7.9 Hz, 2H), 5.80 (s, 1H), 2.33 (s, 3H), 2.25 (s, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 144.1, 141.1, 137.4, 129.3, 128.6, 127.6, 126.7, 126.6, 76.2, 21.2.




***(4-Fluorophenyl)(4-methoxyphenyl)methanol (1.39):*** This compound was synthesized from *p*-bromoanisole and *p*-fluorobenzaldehyde according to the general procedure **GP2** as a yellow oil in quantitative yield. The obtained $^{1}$H NMR data are in agreement with those previously reported in the literature. On the other hand, $^{13}$C NMR data are not in agreement with the literature because the authors did not consider coupling constants between $^{13}$C and $^{19}$F nuclei in benzene ring.[49-50] **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 7.00 (t, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.75 (s, 1H), 3.77 (s, 3H), 2.43 (d, *J* = 2.4 Hz, 1H). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 162.2 (d, *J* = 245.7 Hz), 159.3, 139.9, 136.1, 128.2 (d, *J* = 8.0 Hz), 128.0, 115.3 (d, *J* = 21.3 Hz), 114.1, 75.3, 55.4.

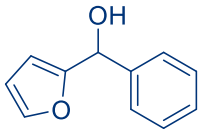



***Ferrocenyl(phenyl)methanol (1.41):*** *Benzoylferrocene* was prepared from ferrocene according the reported procedure[51] followed by $NaBH_4$ reduction (general procedure **GP1**) as an orange solid in 60% yield. The obtained NMR data are in agreement with those previously reported in the literature.[52] **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 2H), 7.36 – 7.29 (m, 2H), 7.28 – 7.22 (m, 1H), 5.47 (d, *J* = 3.2 Hz, 1H), 4.24 – 4.15 (m, 9H), 2.45 (d, *J* = 3.2 Hz, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 143.4, 128.4, 127.6, 126.4, 72.2, 68.6, 68.3, 68.2, 67.6, 66.1.

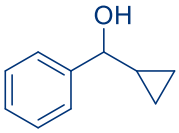



***Phenyl(thiophen-2-yl)methanol (1.43):*** This compound was synthesized from bromobenzene and 2-thiophenecarboxaldehyde according to the general procedure **GP2** and was obtained as a yellow oil in 54% yield. The obtained NMR data are in agreement with those previously reported in the literature.[53] **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.43 (m, 2H), 7.37 (tt, *J* = 8.0, 1.7 Hz, 2H), 7.34 – 7.28 (m, 1H), 7.27 – 7.24 (m, 1H), 6.94 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.89

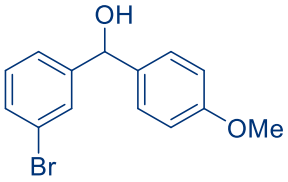
(dt, *J* = 3.5, 1.1 Hz, 1H), 6.06 (d, *J* = 4.0 Hz, 1H), 2.40 (d, *J* = 4.0 Hz, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 148.3, 143.3, 128.7, 128.2, 126.8, 126.4, 125.6, 125.0, 72.6.




***Furan-2-yl(phenyl)methanol (1.45):*** This compound was synthesized from bromobenzene and furfural according to the general procedure **GP2** as yellow oil in 63% yield. The obtained NMR data are in agreement with those previously reported in the literature.[54] **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.26 (m, 6H), 6.29 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.09 (d, *J* = 3.2 Hz, 1H), 5.77 (d, *J* = 3.9 Hz, 1H), 2.64 (s, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 156.1, 142.6, 140.9, 128.5, 128.1, 126.7, 110.3, 107.5, 70.2.



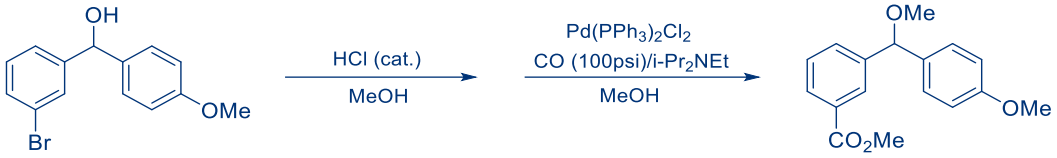

***Cyclopropyl(phenyl)methanol (1.45):*** This compound was synthesized from bromobenzene and cyclopropanecarboxaldehyde according to the general procedure **GP2** as yellow oil in 47% yield. The obtained NMR data are in agreement with those previously reported in the literature.[55] **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.24 (m, 5H), 4.01 (d, *J* = 8.3 Hz, 1H), 2.01 (s, 1H), 1.28 – 1.17 (m, 1H), 0.68 – 0.33 (m, 4H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 143.9, 128.5, 127.6, 126.1, 78.6, 19.3, 3.7, 2.9.




***(3-Bromophenyl)(4-methoxyphenyl)methanol[56] (1.49):*** This compound was synthesized from *p*-bromoanisole and 3-bromobenzaldehyde according to the general procedure **GP2** as colourless oil in 98% yield. The obtained NMR data are in agreement with those previously reported in the literature.[56] **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.52 (t, *J* = 1.6 Hz, 1H), 7.36 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.27 – 7.19 (m, 3H), 7.16 (t, *J* = 7.8 Hz, 1H), 6.87 – 6.80 (m, 2H), 5.68 (s, 1H), 3.76 (s, 3H), 2.50 (s, 1H); **$^{13}$C NMR** (100 MHz,

$CDCl_3$) δ 159.3, 146.4, 135.6, 130.5, 130.1, 129.5, 128.1, 125.1, 122.7, 114.1, 75.2, 55.4.

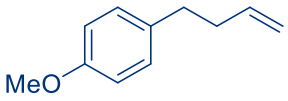
***Methyl 3-(methoxy(4-methoxyphenyl)methyl)benzoate (1.51):***



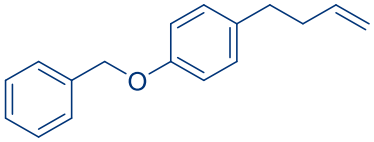

This compound was prepared by methylation of **8i** using modified procedure[57], followed by carbonylation. A solution of previously prepared bromide (1 eq., 250 mg, 0.8 mmol), i-$Pr_2Et$ (1.2 eq., 976 μL, 0.98 mmol) and $Pd(PPh_3)_2Cl_2$ (2 mol%, 14.3 mg, 0.02 mmol) in MeOH (5 mL) was heated at 100 °C under CO (100 psi) for 20 hours. The reaction mixture was filtered, concentrated *in vacuo* and purified by flash chromatography. Yellow oil. Yield 62%. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.03 (t, *J* = 1.8 Hz, 1H), 7.92 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.55 – 7.52 (m, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.27 – 7.22 (m, 2H), 6.89 – 6.83 (m, 2H), 5.24 (s, 1H), 3.90 (s, 3H), 3.78 (s, 3H), 3.36 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 167.2, 159.3, 143.1, 133.8, 131.3, 130.4, 128.7, 128.6, 128.4, 128.0, 114.0, 84.6, 57.0, 55.4, 52.2; **HRMS (EI):** Exact mass calcd for $C_{17}H_{19}O_4$ $(M+H)^+$: 287.1283, Found: 287.1273; **MS (ESI):** $(M)^+$; **IR (NaCl):** 3420, 2992, 2903, 2666, 2048, 1940, 1722, 1612, 1510, 1248, 1173.

*1.4.2 General procedure for the scandium pre-catalysed deoxygenative allylation (**GP3**)*

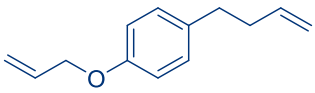
To a 1-dram vial with benzylic alcohol (1 mmol, 1 eq.) in acetonitrile (2 mL), scandium triflate (0.05 mmol, 5 mol%) was added, followed by allyltrimethylsilane (4 mmol, 4 eq.). The reaction was stirred at 40 °C for 15-45 minutes until the starting material was consumed based on TLC analysis. The reaction mixture was concentrated *in vacuo* and subjected to flash column chromatography on silica gel.



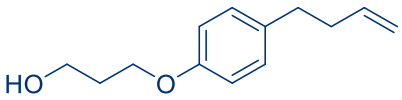

***1-(But-3-en-1-yl)-4-methoxybenzene (1.2):*** Obtained using the general procedure **GP3** in 77% yield as a clear oil. The obtained NMR data are in agreement with those previously reported in the literature.[58] **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.16 – 7.04 (m, 1H), 6.86 – 6.77 (m, 1H), 5.91 – 5.78 (m, 1H), 5.09 – 4.91 (m, 1H), 3.77 (s, 1H), 2.68 – 2.61 (m, 1H), 2.38 – 2.27 (m, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 157.9, 138.3, 134.1, 129.4, 115.0, 113.8, 55.3, 35.9, 34.6.



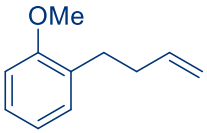

**1-(Benzyloxy)-4-(but-3-en-1-yl)benzene (1.6):** Obtained using the general procedure **GP3** in 97% yield as a pale-yellow oil. The obtained NMR data are in agreement with those previously reported in the literature.[59] **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.29 (m, 5H), 7.14 – 7.07 (m, 2H), 6.93 – 6.88 (m, 2H), 5.86 (ddt, *J* = 16.8, 10.3, 6.5 Hz, 1H), 5.08 – 4.96 (m, 4H), 2.69 – 2.63 (m, 2H), 2.35 (dd, *J* = 14.8, 7.3 Hz, 2H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 157.1, 138.3, 137.4, 134.4, 129.5, 128.7, 128.0, 127.6, 115.0, 114.8, 70.2, 35.9, 34.6.



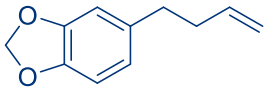
***1-(Allyloxy)-4-(but-3-en-1-yl)benzene (1.8):*** Obtained using the general procedure **GP3** in 94% yield as a clear oil as a pale yellow oil. The obtained NMR data are in agreement with those previously reported in the literature.[60] **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.12 – 7.06 (m, 2H), 6.87 – 6.81 (m, 2H), 6.11 – 6.00 (m, 1H), 5.85 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.45 – 5.35 (m, 1H), 5.31 – 5.23 (m, 1H), 5.08 – 4.93 (m, 2H), 4.51 (d, *J* = 5.3 Hz, 2H), 2.68 – 2.61 (m, 2H), 2.34 (dt, *J* = 14.3, 7.1 Hz, 2H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 156.9, 138.3, 134.3, 133.6, 129.4, 117.6, 115.0, 114.7, 69.0, 35.9, 34.6.



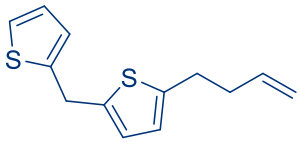
***3-(4-(But-3-en-1-yl)phenoxy)propan-1-ol (1.10):*** Obtained using the general procedure **GP3** in 51% yield as a colourless oil**.** **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.09 – 7.03 (m, 2H), 6.83 – 6.76 (m, 2H), 5.81 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H), 5.04 – 4.89 (m, 2H), 4.06 (t, *J* = 5.7 Hz, 2H), 3.81 (t, *J* = 5.7 Hz, 2H), 2.67 – 2.56 (m, 2H), 2.34 – 2.26 (m, 2H), 1.99 (p, *J* = 5.7 Hz, 2H), 1.85 (s, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 157.0, 138.3, 134.4, 129.5, 115.0, 114.5, 66.1, 60.9, 35.9, 34.6, 32.1; **HRMS (EI):** Exact mass calcd for $C_{13}H_{19}O_2$ $(M+H)^+$: 207.1385, Found: 207.1374; **MS (ESI):** 207.28 $(M+H)^+$; **IR (NaCl):** 3414, 3397, 1612, 1508, 1474, 1389, 1240.



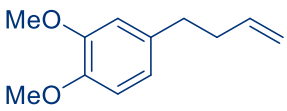
***1-(But-3-en-1-yl)-2-methoxybenzene (1.15):*** Obtained using the general procedure **GP3** in 24% yield as a clear oil. The obtained NMR data are in agreement with those previously reported in the literature.[61] **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.21 – 7.10 (m, 2H), 6.91 – 6.83 (m, 2H), 5.88 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.08 – 4.93 (m, 2H), 3.82 (s, 3H), 2.74 – 2.67 (m, 2H), 2.38 – 2.30 (m, 2H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 157.6, 138.9, 130.4, 130.0 (s), 127.2, 120.4, 114.6, 110.4, 55.4, 34.0, 29.9.



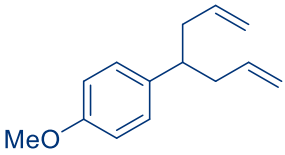
***5-(But-3-en-1-yl)benzo[d][1,3]dioxole (1.19):*** Obtained using the general procedure **GP3** in 10% yield as a colourless oil. The obtained NMR data are in agreement with those previously reported in the literature.[58] **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 6.76 – 6.61 (m, 3H), 5.92 (s, 2H), 5.91 – 5.78 (m, 1H), 5.07 – 4.94 (m, 2H), 2.65 – 2.61 (m, 2H), 2.38 – 2.28 (m, 2H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 147.6, 145.7, 138.1, 135.9, 121.3, 115.1, 109.0, 108.2, 100.9, 35.9, 35.3.



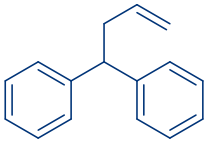
***2-(But-3-en-1-yl)thiophene (1.29):*** Obtained using the general procedure **GP3** in 41% yield as a colourless oil. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.17 – 7.12 (m, 1H), 6.94 – 6.90 (m, 1H), 6.88 – 6.85 (m, 1H), 6.66 (d, *J* = 3.5 Hz, 1H), 6.60 (d, *J* = 3.5 Hz, 1H), 5.84 (ddt, *J* = 16.9, 10.3, 6.6 Hz, 1H), 5.10 – 4.96 (m, 2H), 4.27 (s, 2H), 2.87 – 2.80 (m, 2H), 2.43 – 2.34 (m, 2H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 143.8, 143.5, 140.9, 137.6, 126.9, 125.3, 124.9, 124.2, 123.9, 115.5, 35.7, 30.6, 29.8; **MS (ESI):** 235.17 $(M+H)^+$; **IR (NaCl):** 3008, 2976, 2922, 1639, 1487, 1431.



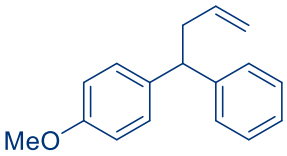
***4-(But-3-en-1-yl)-1,2-dimethoxybenzene (1.25):*** Obtained using the general procedure **GP3** in 15% yield as a colourless oil. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 6.84 – 6.66 (m, 3H), 5.86 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.14 – 4.93 (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 2.71 – 2.60 (m, 2H), 2.40 – 2.33 (m, 2H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 148.8, 147.3, 138.2, 134.6, 120.3, 115.0, 111.9, 111.3, 56.0, 55.9, 35.8, 35.1; **HRMS (EI):** Exact mass calcd for $C_{12}H_{17}O_2$ $(M+H)^+$: 193.1229, Found: 193.1217; **MS (ESI):** 193.13 $(M+H)^+$; **IR (NaCl):** 3443, 2066, 1638, 1516, 1464, 1261, 1234.



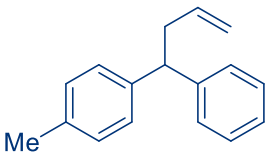

***1-(Hepta-1,6-dien-4-yl)-4-methoxybenzene (1.27):*** Obtained using the general procedure **GP3** in 76% yield as a colourless oil. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.10 – 7.04 (m, 2H), 6.86 – 6.81 (m, 2H), 5.66 (ddt, *J* = 17.3, 10.1, 7.0 Hz, 2H), 5.00 – 4.89 (m, 4H), 3.78 (s, 3H), 2.72 – 2.62 (m, 1H), 2.44 – 2.26 (m, 4H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 158.0, 137.1, 136.8, 128.7, 116.1, 113.7, 55.3, 44.9, 40.6.



***But-3-ene-1,1-diyldibenzene (1.34):*** Obtained using the general procedure **GP3** in 96% yield as a colourless oil. The obtained NMR data are in agreement with those previously reported in the literature.[62] **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.31 – 7.21 (m, 8H), 7.20 – 7.13 (m, 2H), 5.72 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.07 – 4.91 (m, 2H), 4.00 (t, *J* = 7.9 Hz, 1H), 2.84 – 2.79 (m, 2H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 144.6, 137.0, 128.5, 128.1, 126.3, 116.4, 51.4, 40.1.

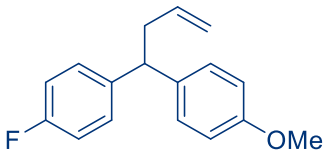



***1-Methoxy-4-(1-phenylbut-3-en-1-yl)benzene (1.36):*** Obtained using the general procedure **GP3** in 94% yield as a colourless oil. The obtained NMR data are in agreement with those previously reported in the literature.[63] **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.30 – 7.12 (m, 7H), 6.85 – 6.79 (m, 2H), 5.71 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.07 – 4.90 (m, 2H), 3.96 (t, *J* = 7.9 Hz, 1H), 3.76 (s, 3H), 2.78 (t, *J* = 7.3 Hz, 2H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 158.1, 145.1, 137.1, 136.8, 129.0, 128.5, 128.0, 126.2, 116.3, 113.9, 55.3, 50.5, 40.3.

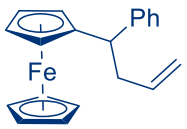



***1-Methyl-4-(1-phenylbut-3-en-1-yl)benzene (1.38):*** Obtained using the general procedure **GP3** in 95% yield as a colourless oil. The obtained NMR data are in agreement with

those previously reported in the literature.[63] **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.31 – 7.19 (m, 4H), 7.19 – 7.05 (m, 5H), 5.72 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.03-4.95 (m, 2H), 3.97 (t, *J* = 7.9 Hz, 1H), 2.79 (t, *J* = 7.3 Hz, 2H), 2.29 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 144.9, 141.6, 137.1, 135.8, 129.2, 128.5, 128.0, 128.0, 126.2, 116.3, 51.0, 40.1, 21.1.

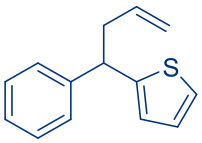



***1-Fluoro-4-(1-(4-methoxyphenyl)but-3-en-1-yl)benzene (1.40):*** Obtained using the general procedure **GP3** in 84% yield as a yellow solid. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.21 – 7.09 (m, 4H), 6.99 – 6.91 (m, 2H), 6.85 – 6.80 (m, 2H), 5.75 – 5.63 (m, 1H), 5.07 – 4.91 (m, 2H), 3.95 (t, *J* = 7.9 Hz, 1H), 3.77 (s, 3H), 2.78 – 2.72 (m, 2H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 161.4 (d, *J* = 244.1 Hz), 158.1, 140.7 (d, *J* = 3.2 Hz), 136.8, 136.6, 129.3 (d, *J* = 7.8 Hz), 128.9, 116.5, 115.2 (d, *J* = 21.0 Hz), 114.0, 55.3, 49.7, 40.4; **HRMS (EI):** Exact mass calcd for $C_{17}H_{18}OF$ $(M+H)^+$: 257.1342; Found: 257.1344; **MS (ESI):** 279.38 $(M+Na)^+$; **IR (NaCl):** 3416. 1634, 1504, 1296, 1223. **Melting point:** 41.4-43.5 °C.

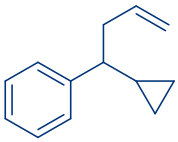



***(1-Ferrocenylbut-3-en-1-yl)benzene (1.42):*** Obtained using the general procedure **GP3** in 93% yield as an orange solid. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 2H), 7.20 – 7.14 (m, 3H), 5.69 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H), 5.03 – 4.89 (m, 2H), 4.18 (dt, *J* = 2.4, 1.3 Hz, 1H), 4.10 (td, *J* = 2.4, 1.3 Hz, 1H), 4.06 (s, 5H), 4.05 (td, *J* = 2.3, 1.2 Hz, 1H), 3.95 (dt, *J* = 2.5, 1.3 Hz, 1H), 3.68 (dd, *J* = 10.3, 4.7 Hz, 1H), 2.88 – 2.80 (m, 1H), 2.66 – 2.56 (m, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 145.0, 137.2, 128.3, 128.1, 126.3, 116.0, 93.9, 68.7, 67.7 (d, *J* = 10.2 Hz), 67.1 (d, *J* = 3.6 Hz), 46.4, 41.6; **HRMS (EI):** Exact mass calcd for $C_{20}H_{20}Fe$ $(M)^+$: 316.0914, Found: 316.0912; **MS (ESI):** 316.41 $(M)^+$; **IR (NaCl):** 3451, 3071, 3022, 1489, 1445, 1232, 1178, 1101; **Melting point:** 46.8-49.1

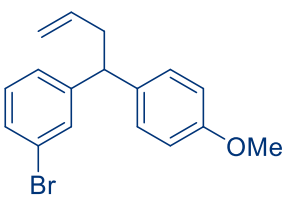
°C.




***2-(1-Phenylbut-3-en-1-yl)thiophene (1.44):*** Obtained using the general procedure **GP3** in 52% yield as a yellow oil. The obtained NMR data are in agreement with those previously reported in the literature.[64] **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.16 (m, 5H), 7.12 (dt, *J* = 2.0, 0.9 Hz, 1H), 6.90 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.83 (dt, *J* = 3.2, 0.9 Hz, 1H), 5.72 (ddt, *J* = 17.0, 10.2, 6.9 Hz, 1H), 5.09 – 4.93 (m, 2H), 4.22 (t, *J* = 7.8 Hz, 1H), 2.93 – 2.73 (m, 2H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 148.9, 144.1, 136.3, 128.6, 127.9, 126.8, 126.6, 124.1, 123.7, 116.9, 47.0, 41.7.

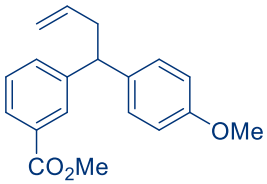


**(1-Cyclopropylbut-3-en-1-yl)benzene (*1.48*):** Obtained using the general procedure **GP3** in 48% yield as a colourless oil. The obtained NMR data are in agreement with those previously reported in the literature.[17] **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 2H), 7.23 – 7.16 (m, 3H), 5.80 – 5.67 (m, 1H), 5.03 – 4.87 (m, 2H), 2.62 – 2.44 (m, 2H), 1.88 (dt, *J* = 11.3, 7.2 Hz, 1H), 1.07 – 0.94 (m, 1H), 0.65 – 0.56 (m, 1H), 0.44 – 0.34 (m, 1H), 0.29 – 0.19 (m, 1H), 0.14 – 0.03 (m, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 145.3, 137.2, 128.3, 127.7, 126.1, 115.7, 51.1, 41.3, 17.2, 5.8, 3.9.

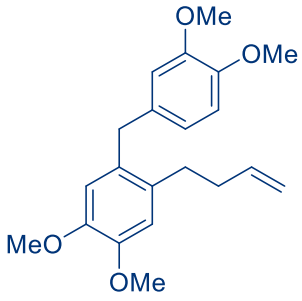



***1-Bromo-3-(1-(4-methoxyphenyl)but-3-en-1-yl)benzene (1.50):*** Obtained using the general procedure **GP3** in 94% yield as a colourless oil. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.31 – 7.27 (m, 1H), 7.16 – 7.09 (m, 4H), 6.86 – 6.80 (m, 2H), 5.68

(ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.06 – 4.92 (m, 2H), 3.92 (t, *J* = 7.9 Hz, 1H), 3.76 (s, 3H), 2.78 – 2.72 (m, 2H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 158.2, 147.5, 136.5, 135.9, 131.0, 130.1, 129.3, 128.9, 126.7, 122.6, 116.7, 114.0, 55.3, 50.2, 40.0; **HRMS (EI):** Exact mass calcd for $C_{17}H_{18}O^{79}Br$ $(M+H)^+$: 317.0541, Found: 317.0565; **MS (ESI):** 317.65 $(M+H)^+$; **IR (NaCl):** 3422, 3074, 2833, 1639, 1610, 1510, 1474, 1250.

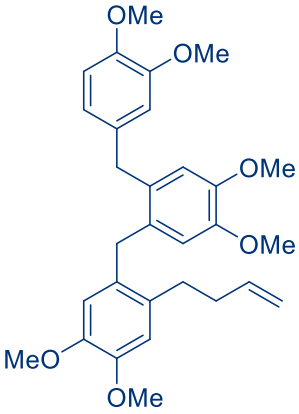



***Methyl 3-(1-(4-methoxyphenyl)but-3-en-1-yl)benzoate (1.52):*** Obtained using the general procedure **GP3** in 97% yield as a colourless oil. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.93 (t, *J* = 1.7 Hz, 1H), 7.85 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.42 – 7.37 (m, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.17 – 7.12 (m, 2H), 6.85 – 6.80 (m, 2H), 5.69 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.06 – 4.92 (m, 2H), 4.02 (t, *J* = 7.9 Hz, 1H), 3.89 (s, 3H), 3.76 (s, 3H), 2.82 – 2.78 (m, 2H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 167.3, 158.2, 145.4, 136.6, 136.2, 132.7, 130.4, 129.0, 128.9, 128.6, 127.6, 116.7, 114.0, 55.3, 52.2, 50.3, 40.1; **HRMS (EI):** Exact mass calcd for $C_{19}H_{21}O_3$ $(M+H)^+$: 297.1491, Found: 297.1515; **MS (ESI):** 297.23 $(M+H)^+$; **IR(NaCl):** 3427, 2999, 2949, 2928, 2062, 1720, 1610, 1510, 1435, 1281.

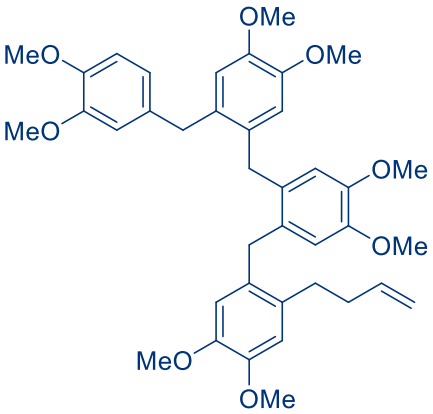



***1-(But-3-en-1-yl)-2-(3,4-dimethoxybenzyl)-4,5-dimethoxybenzene (1.30):*** Obtained using the general procedure **GP3** in 5% yield as a yellow oil. **$^{1}$H NMR** (400 MHz, $C_6D_6$) δ 6.75 – 6.58 (m, 5H), 5.82 (ddt, *J* = 16.9, 10.1, 6.5 Hz, 1H), 5.09 – 4.94 (m, 2H), 3.91 (s, 2H), 3.50 (s, 3H), 3.44 (s, 3H), 3.43 (s, 3H), 3.42 (s, 3H), 2.69 – 2.64 (m, 2H), 2.25 (dt, *J* = 14.6, 7.2 Hz, 2H); **$^{13}$C NMR** (100 MHz, $C_6D_6$) δ 150.3, 148.9, 148.7, 148.6, 138.6, 134.3, 132.7, 131.2, 121.0, 115.4, 115.0, 114.3, 113.3, 112.6, 55.9 (2 C), 55.7, 55.6,

38.5, 35.8, 32.5; **HRMS (EI):** Exact mass calcd for $C_{21}H_{26}O_4Na$ $(M+Na)^+$: 365.1729, Found: 365.1739; **MS (ESI):** 365.41 $(M+Na)^+$; **IR (NaCl):** 2934, 1637, 1606, 1514, 1463, 1259, 1029.




***1-(But-3-en-1-yl)-2-(2-(3,4-dimethoxybenzyl)-4,5-dimethoxybenzyl)-4,5-dimethoxybenzene (1.31):*** Obtained using the general procedure **GP3** in 4% yield as a yellow oil. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 6.77 (d, *J* = 7.8 Hz, 1H), 6.70 (d, *J* = 1.2 Hz, 2H), 6.63 – 6.59 (m, 2H), 6.46 (s, 1H), 6.41 (s, 1H), 5.76 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 4.99 – 4.90 (m, 2H), 3.89 – 3.78 (m, 16H), 3.71 (s, 3H), 3.70 (s, 3H), 2.52 (dd, *J* = 9.1, 6.7 Hz, 2H), 2.25 – 2.14 (m, 2H); ); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 149.0, 147.5, 147.4, 147.3 (2 C), 147.2, 138.2, 133.4, 132.4, 131.3, 131.1, 130.2, 120.6, 115.0, 113.9, 113.3 (2 C), 112.8, 112.0, 111.3, 56.1, 56.0 (4 C), 55.9, 38.4, 35.1 (2 C), 32.2; **HRMS (EI):** Exact mass calcd for $C_{30}H_{36}O_6Na$ $(M+Na)^+$: 515.2410, Found: 515.2403; **MS (ESI):** 515.63 $(M+Na)^+$; **IR (NaCl):** 2934, 1639, 1514, 1464, 1257, 1028.



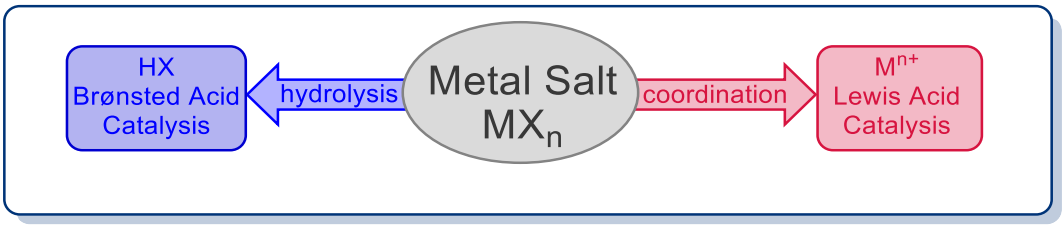

***1-(But-3-en-1-yl)-2-(2-(2-(3,4-dimethoxybenzyl)-4,5-dimethoxybenzyl)-4,5-dimethoxybenzyl)-4,5-dimethoxy benzene (1.32):*** Obtained using the general procedure **GP3** in 5% yield as a yellow oil. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 6.72 (d, *J* = 8.1 Hz, 1H), 6.68 (s, 2H), 6.60 – 6.52 (m, 2H), 6.51 – 6.43 (m, 3H), 6.39 (s, 1H), 5.74 (ddt, *J* = 16.9,

10.3, 6.6 Hz, 1H), 4.98 – 4.89 (m, 2H), 3.87 (s, 3H), 3.84 – 3.65 (m, 27H), 2.51 – 2.46 (m, 2H), 2.22 – 2.13 (m, 2H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 149.0, 147.6, 147.4 (4 C), 147.3, 147.2, 138.1, 133.2, 132.4, 131.3 (2 C), 130.9, 130.8, 130.0, 120.6, 115.1, 113.9, 113.4, 113.2 (2 C), 113.1, 112.8, 112.0, 111.2, 56.1 (2 C), 56.0 (5 C), 55.9, 38.4, 35.4, 35.1, 35.0, 32.2; **HRMS (EI):** Exact mass calcd for $C_{39}H_{46}O_8Na$ $(M+Na)^+$: 665.3090, Found: 665.3082; **MS (ESI):** 665.81 $(M+Na)^+$; **IR (NaCl):** 2934, 1637, 1608, 1514, 1279, 1138, 1029.

# Chapter 2

# Testing the veracity of claims of Lewis acid catalysis

Different reactions reported earlier in the literature have been examined by addition of 2,6-di-*tert*-butyl-4-methylpyridine. This simple test allow us to reveal the correct reaction pathway.



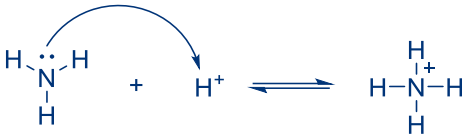
## 2.1 Introduction

Acid-catalyzed reactions are well-studied reactions and play an important role in organic chemistry. Acid and bases are usually classified according to three different definitions. The oldest (1884) and simplest definition is by Swedish scientist Svante Arrhenius.[65] He defined acids as substances which in solution produce hydrogen ($H^+$) ions. Similarly, he defined bases as substances which in solution produce hydroxide ($OH^-$) ions. The disadvantage of this theory is that is applicable only to aqueous solutions.

In 1923, another acid-base theory was proposed independently by Danish chemist Johannes Nicolaus Brønsted and English chemist Thomas M. Lowry.[65] According to their names, this theory has been called Brønsted-Lowry acid-base theory. Although, since Brønsted gave the most explicit statement of this theory, in the literature is commonly known as the Brønsted acid-base theory. According to this theory, acids are substances which can release hydrogen ion (proton donor), and bases are substances which can accept hydrogen ion (proton acceptor), hence the theory can be extended to non-aqueous systems (**Scheme 2.1**).


***Scheme 2.1***. *Acid-base equilibrium according to Brønsted and Lowry.*

Lastly, the third theory was proposed in the same year (1923) as the previous one by American chemist Gilbert N. Lewis. Lewis theory defines acids as substances which can accept an electron pair (electron pair acceptors), and bases as substances which can donate an electron pair (electron pair donors) as shown in **Scheme 2.2**.[66]



***Scheme 2.2.*** *Acid-base equilibrium according to Lewis.*

Lewis definition is much broader than the previous two and involves more substances. The Arrhenius theory and Brønsted theory actually can be considered as sub-classes of Lewis theory (Figure 2.1). Furthermore, Lewis theory provides a theoretical foundation for Werner's coordination theories.

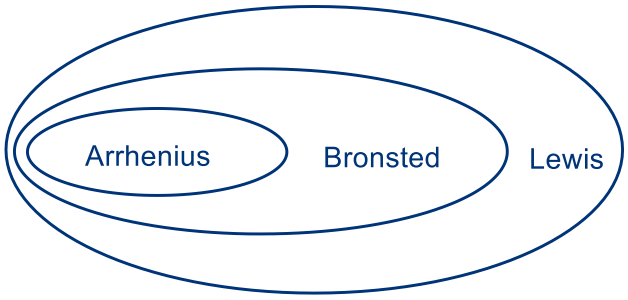



***Figure 2.1.*** *Acid-base hierarchy*

### *2.1.1 Lewis acids in organic chemistry*

Lewis acids are good substitutes for the protic sources in many organic reactions.[67] The need to design Lewis acid species with a special shape and fine-tuned reactivity has become increasingly important in organic chemistry today. Lewis acid catalysis has always been an efficient tool for the formation and breaking of the carbon-carbon and carbon-heteroatom bonds. They have a well-established place in organic synthesis, and a wide variety of Lewis acidic metals are currently in use, i.e. Sc[41, 68], Fe[23, 25], I[20, 69], In[12-15], Ti[21], Bi[16-17], B[9-10] and many others.

### *2.1.2 Lewis acid vs. Brønsted acid catalysis*

It is known that some Lewis acid-catalyzed and Brønsted acid-catalyzed reactions can be ambiguous. The first investigation of reaction mechanisms regarding Lewis vs. Brønsted acid catalysis were carried out by Spencer and coworkers.[38] They

investigated hetero-Michael addition reactions which have been reported to proceed due to activation of a Michael acceptor with a Lewis acid. In their research, 2,6-di-*tert*-butylpyridine was used as a weak base which sequesters protons but does not coordinate to the Lewis acid metal centers due to the bulky *tert*-butyl groups.[39] Interestingly, in the presence of the pyridine base, all tested reactions failed to proceed. Those results have thus led to the conclusion that the reactions were indeed catalyzed from the protons generated in-situ by hydrolysis of metal salts. Following Spencer's work, Hartwig and coworkers expanded the scope of research on metal-catalyzed hydroamination and hydroalkoxylation reactions.[70] Similarly, they found that many of the above studied reactions were catalyzed by strong triflic acid.

In that light, we have conducted a survey of several reported reactions in order to clarify their reaction mechanisms. In a similar fashion, we used 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (**Figure 2.2**)[71] as an alternative to 2,6-di-*tert*-butylpyridine, since it was easier to handle due to its solid form.

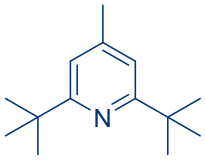
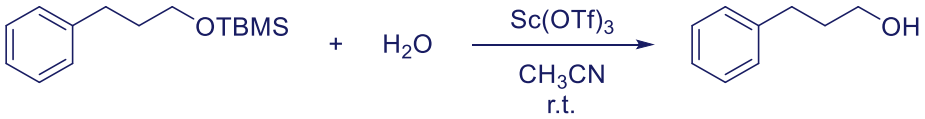



***Figure 2.2****. 2,6-di-tert-butyl-4-methylpyridine (DTBMP)*

## 2.2 Results and discussion[2]

### *2.2.1 Scandium catalysis*

Scandium triflate has been advocated as a water-soluble and water stable Lewis acid.[29] Numerous reactions of its useful activity have been reported.[29] Among others, it has also been used for the deprotection of silyl ethers (**Scheme 2.3**).[40]




***Scheme 2.3.*** *$Sc(OTf)_3$ catalyzed deprotection of silyl ethers*

The reaction was first subjected in the presence of 10 mol% DTBMP base, and results indicated that the reaction does not proceed under those conditions, in contrast to the reaction without DTBMP base added (**Figure 2.3**). Thus, we postulated that the reaction was catalyzed by Brønsted acid as well. Although, the authors performed the test reaction with triflic acid, and due to negative results, they excluded the possibility of a Brønsted acid catalysis. However, their conclusion may be misleading as Hintermann suggested a few years later.[72] They reported that concentrations of acid above trace amount could form a separate inhomogeneous droplet phase, and thus reduce its catalytic activity in the reaction.

[2] Work in subsections 2.2.1, 2.2.2, 2.2.3, 2.2.4 and 2.2.6 was partially contributed by undergraduate student Lin Hong Xuan.

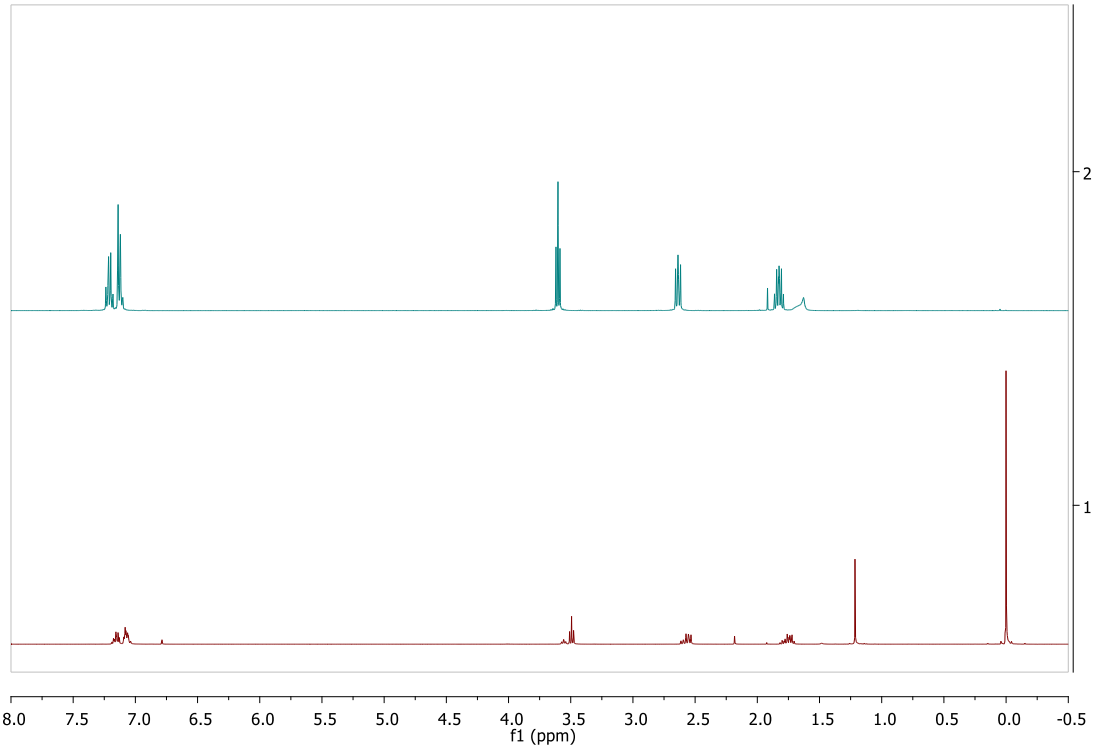
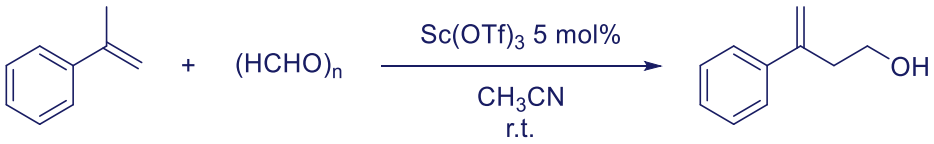



***Figure 2.3.*** *Scandium triflate catalyzed desilylation of TBS ether (Green: without DTBMP; Red: reaction with 10 mol% DTBMP).*

Another reported example of the use of scandium triflate as a Lewis acid catalyst was reported by Saikia and coworkers in the synthesis of primary homoallylic alcohols from alkenes and paraformaldehyde (**Scheme 2.4**).[68] The reported reaction worked well with a variety of aliphatic and aromatic olefins. Hence, we decided to test our hypothesis with their reaction, using prop-1-en-2-ylbenzene as a substrate.




***Scheme 2.4.*** *Synthesis of primary homoallylic alcohols by Saika*

Following their reported procedure, we could obtain the desired homoallylic alcohol product, although in much lower yield (21%) than that was reported (71%). The crude NMR spectrum showed a significant amount of starting material remaining. When DTBMP was added as a base, no product was observed even after we doubled the

reaction time (**Figure 2.4**), indicating once again our hypothesis in this reaction mechanism, that Brønsted acid catalysis takes place. Additionally, the authors also reported that the reaction does not proceed if $Na_2CO_3$ was added as a base, which further supports our hypothesis of Brønsted acid catalysis in the reaction.

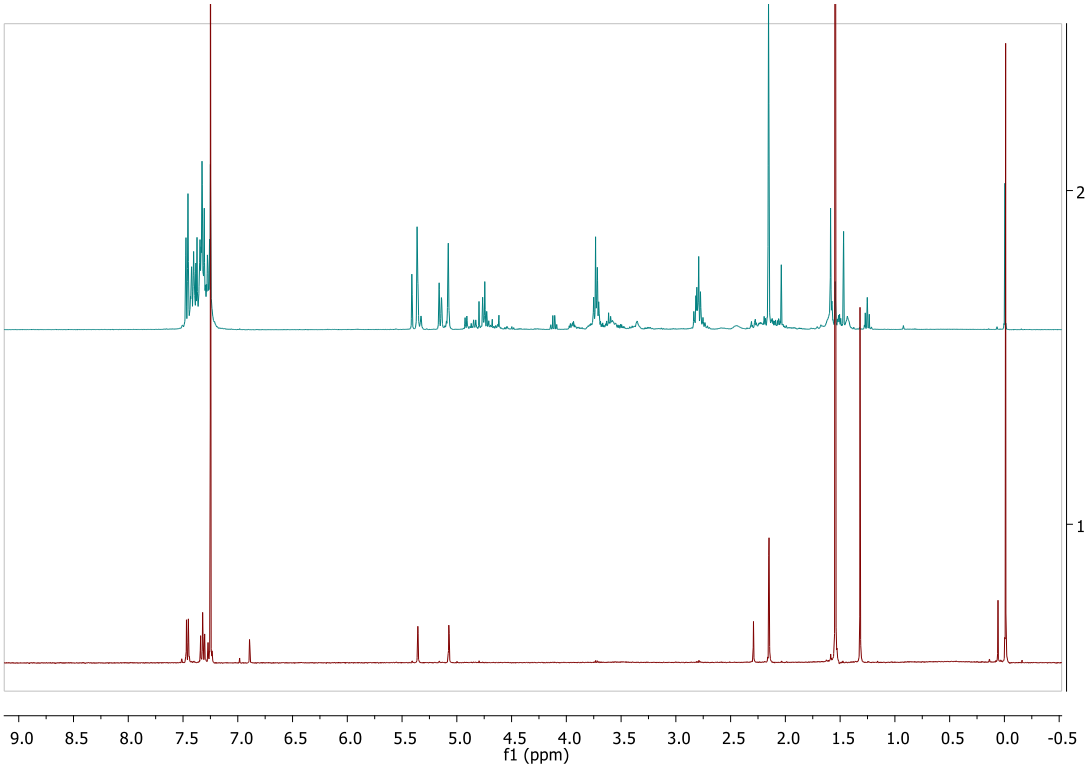



***Figure 2.4.*** *Scandium triflate catalyzed ene reaction (Green: without DTBMP; Red: reaction with 10 mol% DTBMP).*

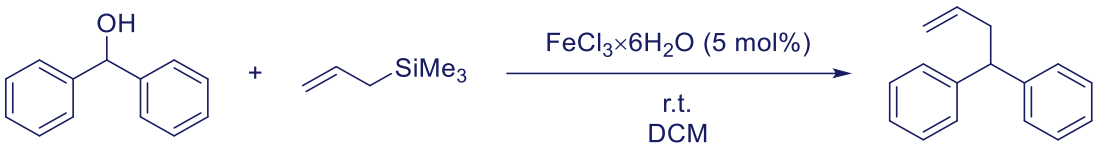
### *2.2.2 Iron-catalyzed allylations*

In recent years, iron catalyzed reaction attracted a great attention in numerous organic transformations. Easily obtained from the nature, abundant, low cost compared to the other Lewis acids and friendly for the environment are some of the reasons of its popularity in organic catalysis.[25]

Iron-catalyzed allylation of benzyl alcohols and benzyl halides were looked into as well.[23] Iron chloride hexahydrate ($FeCl_3 \times 6H_2O$) was used as the catalyst for that

transformation with allyltrimethylsilane, where diaryl methanol substrates gave the best results (**Scheme 2.5**).

Therefore, we chose diphenylmethanol as the substrate for our survey with 10 mol% of DTBMP. In the first experiment following the reported procedure without pyridine base, we observed the formation of desired product.




***Scheme 2.5.*** *Iron chloride catalyzed deoxygenative allylation*

However, reproducibility was not satisfactory due to the formation of dibenzhydryl ether as a side product (Figure 2.5).

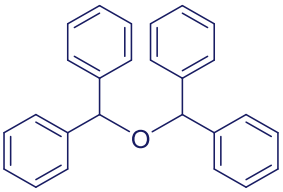



*Figure 2.5. Side product*

In our second experiment, we conducted the reaction under similar conditions, but with 10 mol% of pyridine base as an additive. As expected, NMR analysis of the crude reaction mixture did not show any formation of the desired product (**Figure 2.6**). This experiment shows again that the above-mentioned reaction is catalyzed by a hidden Brønsted acid which is *in situ* generated by hydrolysis of the $FeCl_3 \times 6H_2O$.

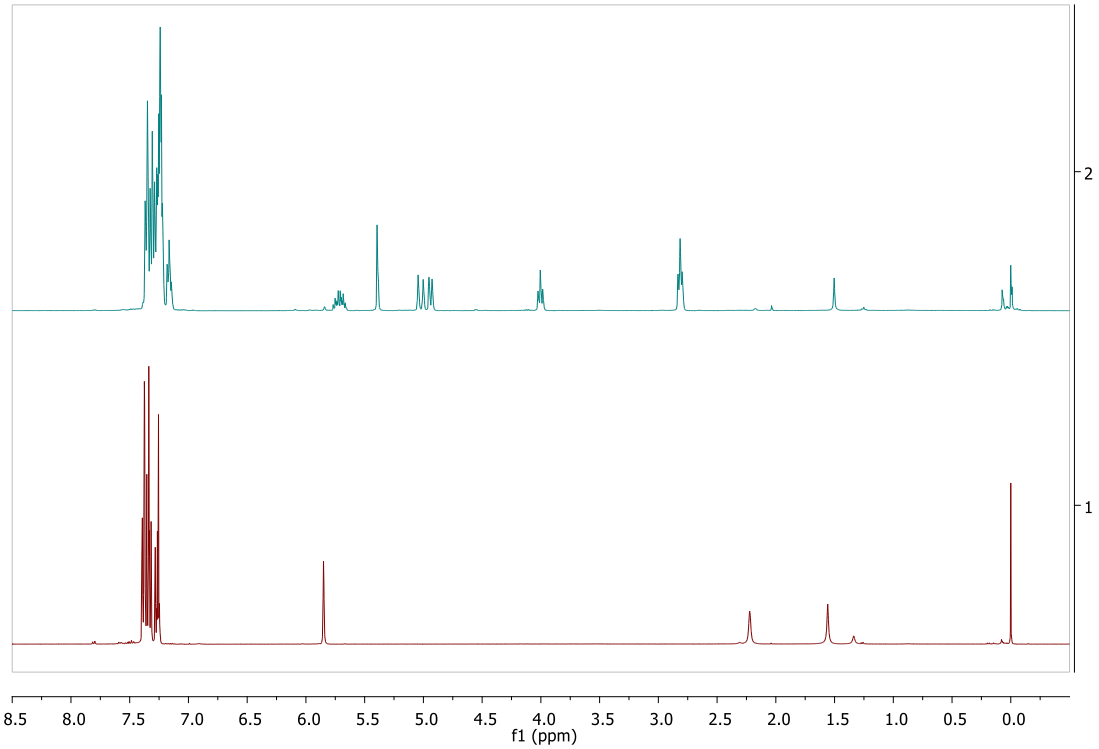



***Figure 2.6.*** *$FeCl_3$ catalyzed deoxygenative allylation (Green: without DTBMP; Red: with 10 mol% DTBMP).*

Another similar reaction was reported by Kim and coworkers in 2011.[25] In their work, they reported iron triflate catalyzed allylation of benzylic acetates with allyltrimethylsilane where the iron triflate was generated *in situ* from mixing iron chloride and silver triflate (**Scheme 2.6**). Similarly, we also decided to test the reaction in the presence of DTBMP.


***Scheme 2.6.*** *$FeCl_3$/AgOTf catalyzed allylation reaction*

Following the initial reported procedure without base, we could observe the formation of the expected product. However, in the presence of the pyridine base, the reaction failed to proceed (Figure 2.7). From that observation, we could also conclude that the

reaction is catalyzed by a Brønsted acid pathway. Furthermore, the authors also observed how the reaction was very effective in the presence of just $FeCl_3$ itself, although the inclusion of AgOTf improve the reaction outcome greatly. In light of our experimental results and the postulation that the reaction proceeds through a hidden Brønsted acid mechanism, the observation made by the authors could be rationalised. Hydrolysis of AgOTf or $Fe(OTf)_3$ *in situ* will produce very strong triflic acid ($pK_a$ ($H_2O$)≈ -15), while hydrolysis of the $FeCl_3$ will produce significantly weaker hydrochloric acid ($pK_a$ ($H_2O$)≈ -6).

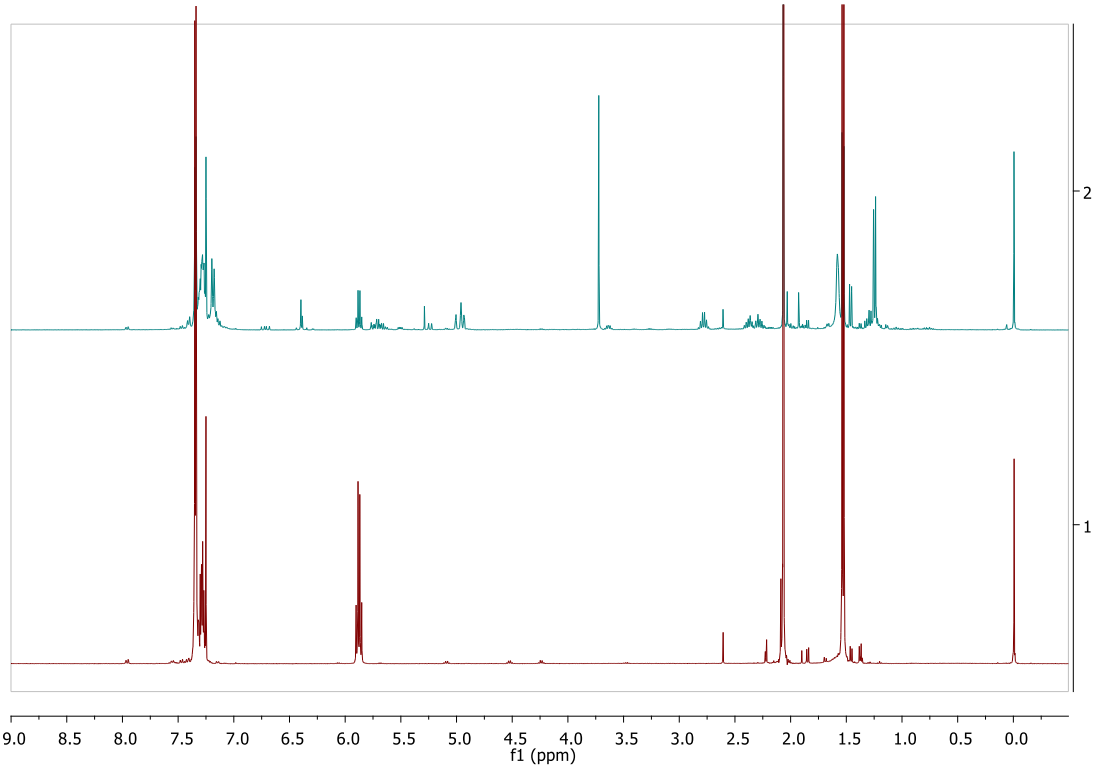
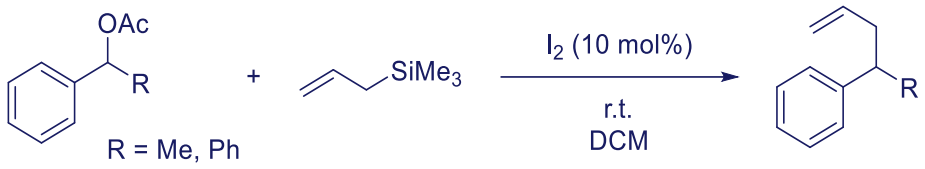



***Figure 2.7.*** *$FeCl_3$/AgOTf catalyzed allylation reaction (Green: without DTBMP; Red: 10 mol% with DTBMP).*

### *2.2.3 Molecular iodine catalyzed allylations*

The use of molecular iodine as an efficient catalyst for the deoxygenative allylation of benzyl acetates with allyltrimethylsilane were reported as well (**Scheme 2.7**).[20] In this

research, the authors observed that the reaction proceeds in the presence of molecular iodine, assuming its Lewis acidic ability.




***Scheme 2.7.*** *Iodine catalyzed allylation*

Once again, we have performed the reported reaction under conditions with and without DTBMP base. In the case of reaction without DTBMP, inspection of the crude NMR spectrum showed formation of desired product as expected. On the other hand, when 10 mol% DTBMP was added, we were unable to detect formation of the desired product (**Figure 2.8**). Therefore, the reaction very likely proceeds through a mechanism catalyzed by Brønsted acid as well. Active acid is probably hydroiodic acid (HI) which is *in situ* generated by iodine hydrolysis (**Scheme 2.8**).


***Scheme 2.8.*** *In-situ iodine hydrolysis*

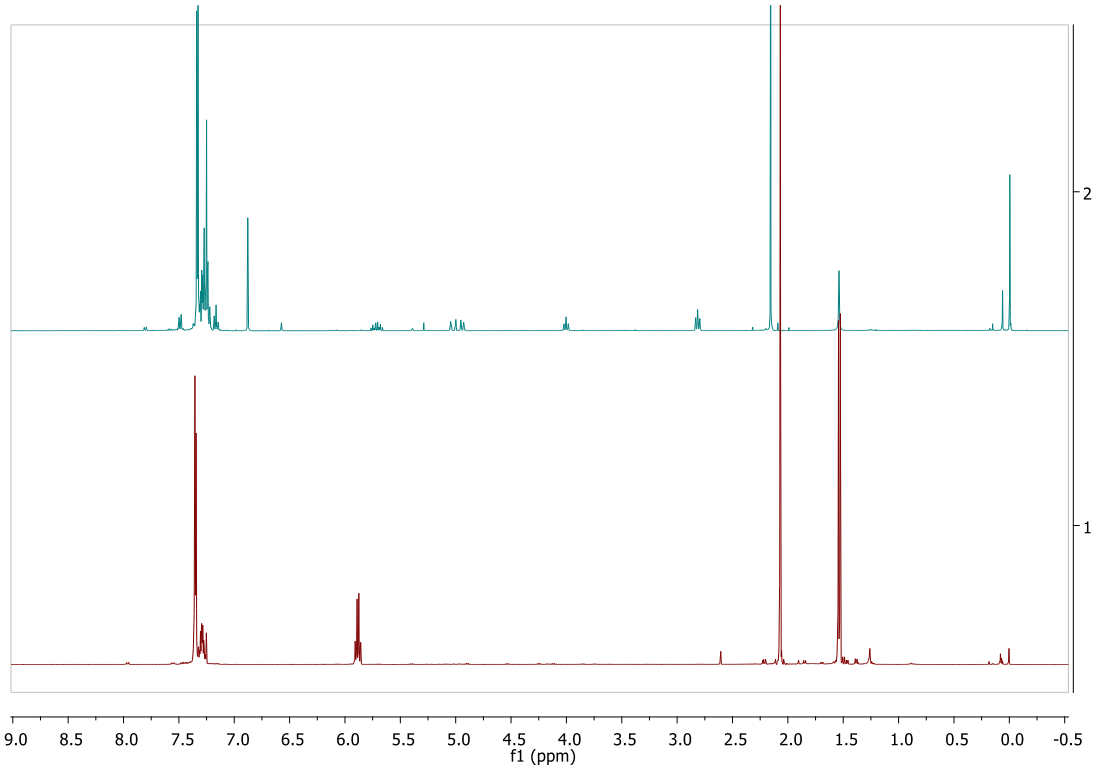
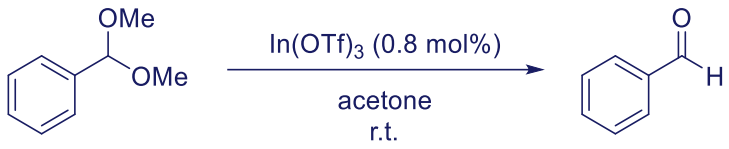



***Figure 2.8.*** *Iodine catalyzed allylation (Green: without DTBMP; Red: with 10 mol% DTBMP).*

### *2.2.4 Indium catalyzed deprotection of acetals*

In recent years, indium catalyzed reactions have become a matter of fashion in organic synthesis. Deprotection of acetals and ketals by indium(III) triflate as a Lewis acid has been reported to be a mild and efficient tool for deprotection of a wide variety of aromatic and aliphatic acetals and ketals.[73] Benzaldehyde dimethyl acetal has been chosen as the substrate for our test reaction (**Scheme 2.9**). For this substrate, the authors reported that the product could be obtained in a high yield (93%) over a short period of time (30 minutes).




***Scheme 2.9.*** *Indium triflate catalyzed deprotection of acetals.*

We were able to reproduce these results following reported procedure. However, in another reaction when 10 mol% DTBMP was added as a base, the reaction was almost completely suppressed as it can be seen on NMR of the crude reaction mixture (Figure 2.9). We could thus conclude that the reaction proceeds through Brønsted acid catalysis.

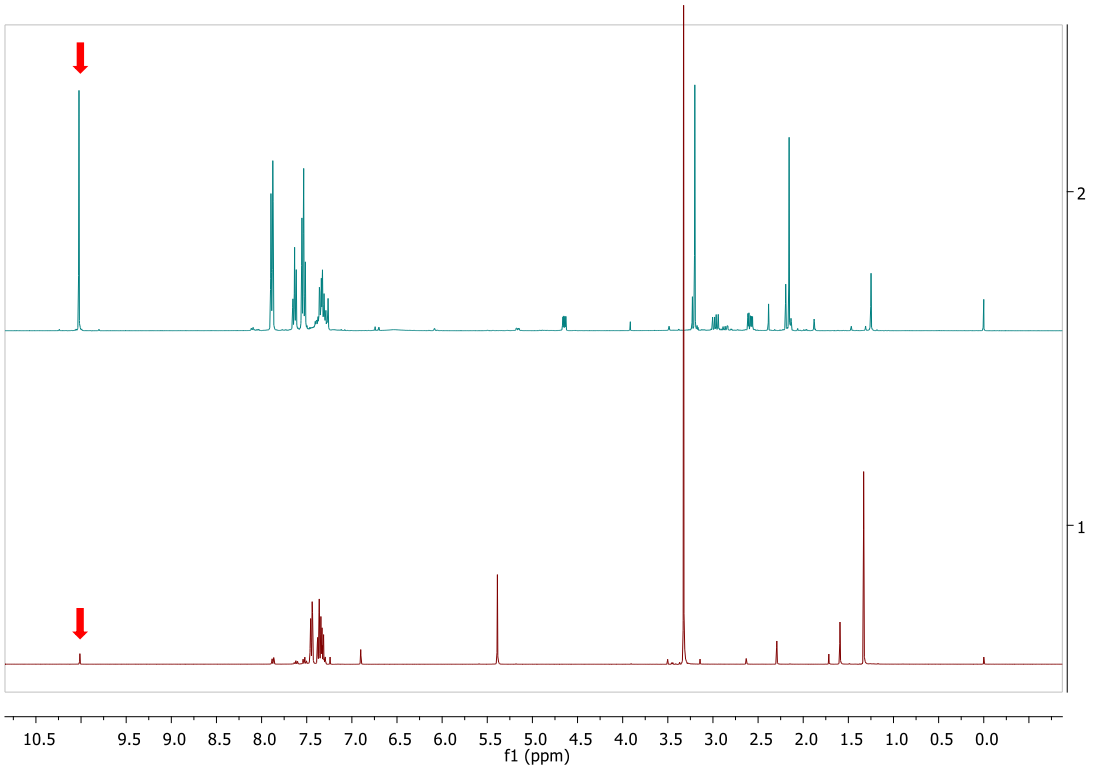
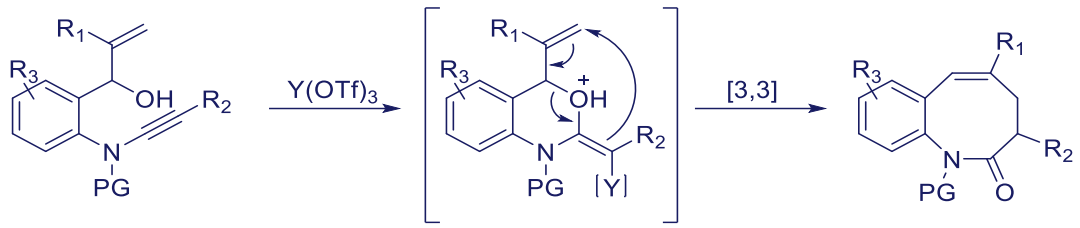



***Figure 2.9.*** *Indium triflate catalyzed deprotection of acetals. (Green: without DTBMP; Red: reaction with 10 mol% DTBMP).*

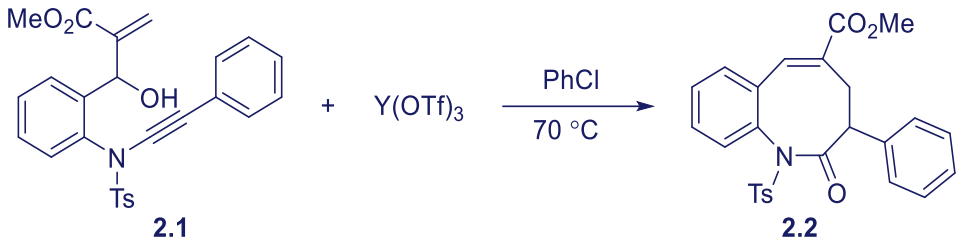
### *2.2.5 Yttrium-catalyzed intramolecular synthesis of medium-sized lactams*

Recently, an interesting methodology on yttrium(III) triflate catalyzed reaction for the synthesis of medium-sized lactams was reported (**Scheme 2.11**).[74] In that work, the method was described as a tandem reaction. To form the desired lactam, the authors suggested that the first step is a catalytic intramolecular hydroalkoxylation of the ynamide group, followed by a Claisen rearrangement. A mechanistic explanation for this reaction is interesting because it suggests yttrium coordination to alkyne (**Scheme 2.10**), which is not common in the chemistry of the rare earth elements.




***Scheme 2.10.*** *Mechanism of the eight-membered ring formation*

Thus, we synthesized the ynamide starting material following reported procedure, and subjected it to the reaction with yttrium triflate.




***Scheme 2.11.*** *Yttrium triflate catalyzed cyclization.*

Results were successfully reproduced using the reported procedure, and interestingly results were reproducible in the presence of DTBMP as well (**Figure 2.10**). Furthermore, the yield was reproducible as well when we changed the solvent to more common acetonitrile, although only 22% conversion was observed in the presence of DTBMP. We tried to achieve the same transformation with pyridinium p-toluenesulfonate (PPTS) as a weak Brønsted acid source, instead of yttrium triflate. To our surprise, the reaction worked, and full conversion was obtained. Combination of these results suggested to us that the reaction is catalyzed by a Brønsted acid mechanism, where the proton source is generated by hydrolysis of yttrium triflate. In the third case, conducting the reaction with PPTS helped us to clarify results of the second case, where the reaction was done with DTBMP. As stated before, PPTS is a commonly used weak acid ($pK_a$ = 5.21) for the organic transformations. Similar to that, the protonated form of DTBMP is also a weak proton source ($pK_a \approx 4.95$). In

addition, the lower conversion observed in the case where the reaction was performed in the presence of DTBMP in acetonitrile was probably due to the solvent effect on $pK_a$ values.

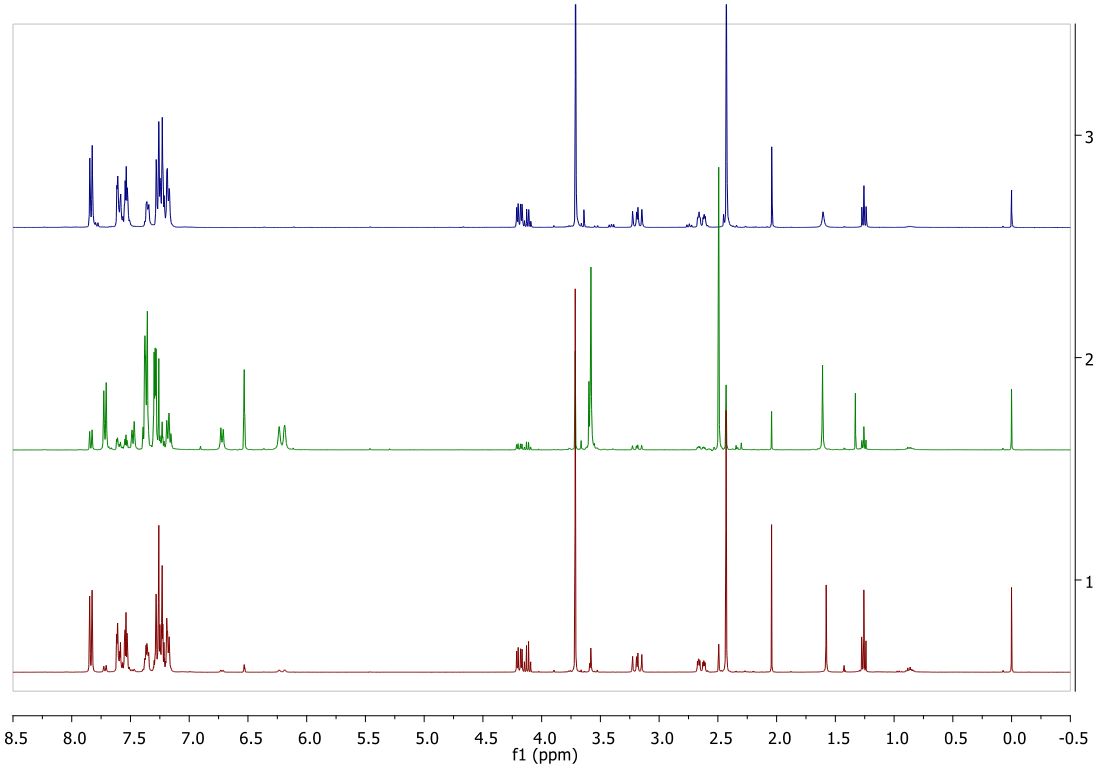



***Figure 2.10.*** *Yttrium catalyzed cyclization (Blue:* ***2.1****, $Y(OTf)_3$ in PhCl; Green:* ***2.1****, $Y(OTf)_3$ and 10 mol% DTBMP in $CH_3CN$; Red:* ***2.1*** *and 10 mol% PPTS in $CH_3CN$).*

### *2.2.6 Halogen bond donor catalysis*

We turned our attention to an interesting claim reported recently which stated that $CBr_4$ shows catalytic activity and can be used as a halogen bond donor for the activation of aldehydes.[75] The authors claimed that weak halogen bond interactions were responsible for the coordination of $CBr_4$ on the oxygen atom of the carbonyl group and therefore activating the corresponding aldehyde (**Figure 2.11**).

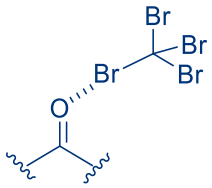
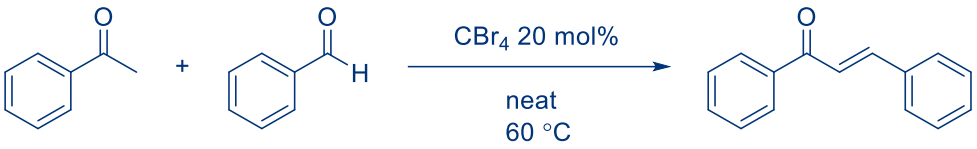



***Figure 2.11.*** *Proposed activation of keto group by halogen bonding catalysis*

Spectroscopic studies in that research did not show presence of other bromine species, and according to that, they rejected the possibility of HBr or Brønsted acid catalysis. Furthermore, they used 10 to 30% HBr in their experiments and lower yields were observed, thus they concluded that HBr was not involved in the reaction. However, these results can lead us back to already mentioned Hinterman's study which can explain lower yields.[72]

To test their claim, we have chosen reaction between benzaldehyde and acetophenone (**Scheme 2.12**).




***Scheme 2.12.*** *$CBr_4$ catalyzed activation of benzaldehydes.*

Following the reported procedure, we were able to obtain the desired α,β-unsaturated ketone (27% conversion calculated from crude NMR). On the other hand, product formation was not observed at all in the experiment with 10 mol% DTBMP as a base (**Figure 2.12**).

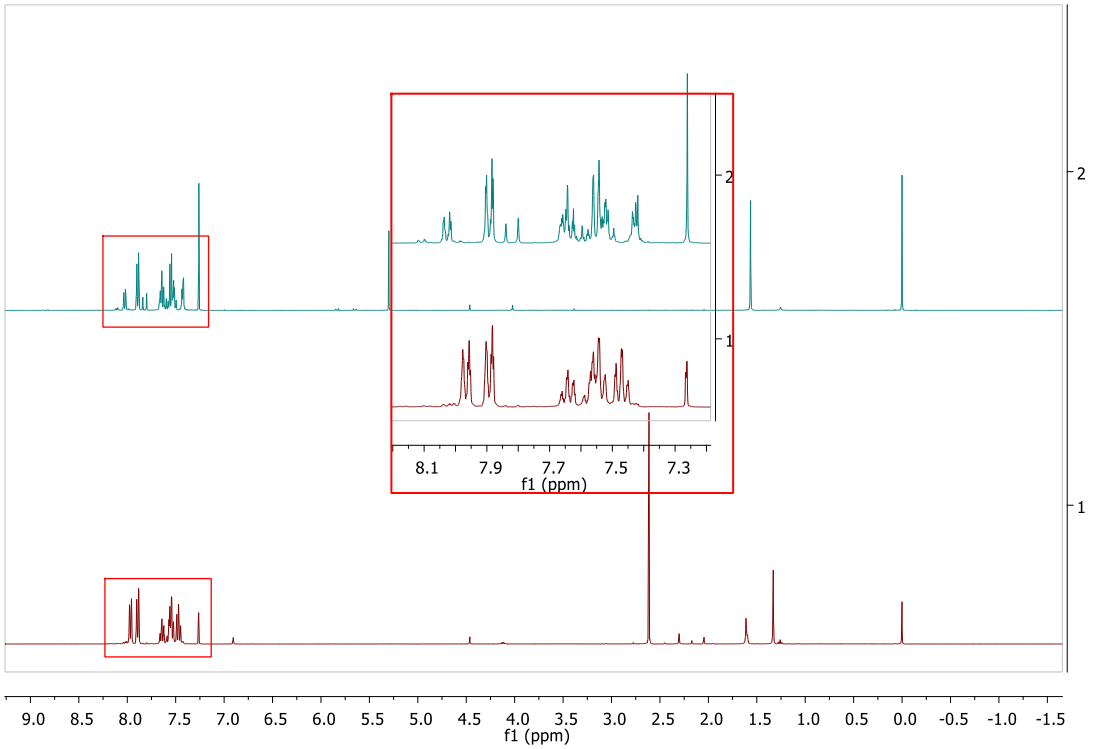
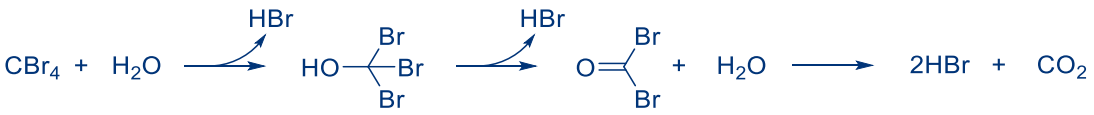



***Figure 2.12.*** *$CBr_4$ catalyzed activation of benzaldehydes (Green: without DTBMP; Red: with 10 mol% DTBMP).*

This result indicates Brønsted acid catalysis within the reaction. The reproducibility problem was likely due to the quality of $CBr_4$. The carbon-bromine bond in $CBr_4$ can break under certain conditions (light, temperature, air, water) especially if not stored properly, e.g. the hydrolysis of $CBr_4$ (**Scheme 2.13**).




***Scheme 2.13.*** *Hydrolysis of $CBr_4$.*

The composition changed in that way could have a great impact on the reaction outcome.

## 2.3 Conclusion

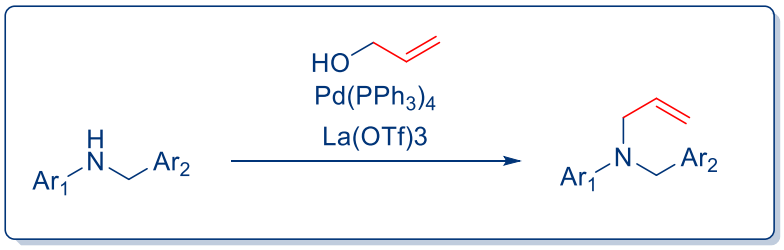
For different reported reactions, the operating mechanism has been tested by using DTBMP. Due to its properties as a bulky and non-nucleophilic base, we could test if reported reactions proceed through Lewis acid catalysis or if it is catalyzed by an in situ generated protons, so-called hidden Brønsted acid. For all of the reactions examined in this chapter, the evidence suggests that the reactions proceed through a hidden Brønsted acid pathway.

In future work, additional tests can be performed by using corresponding acids which will allow further clarification of reaction mechanisms.

# Chapter 3

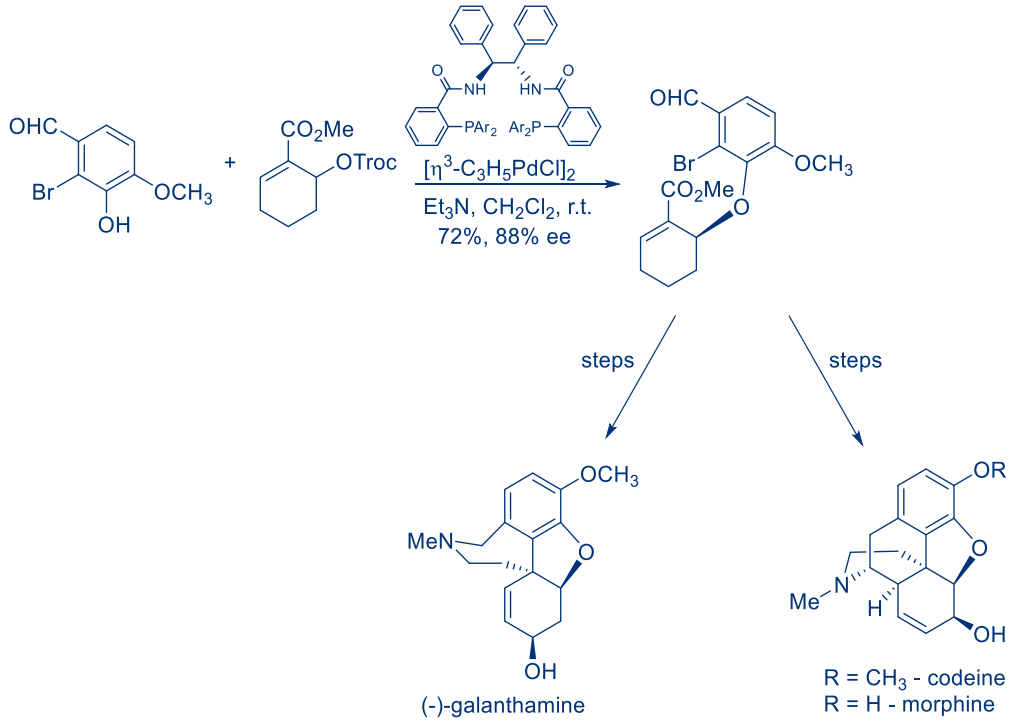
## Bimetallic catalysis in Tsuji-Trost allylation reactions

Different secondary aromatic amines were synthesized and employed in the bimetallic Pd/La-catalyzed Tsuji-Trost type allylation. Underivatized allyl alcohols were used as the allylating agents with lanthanum triflate as a water tolerant Lewis acid for hydroxyl activation.



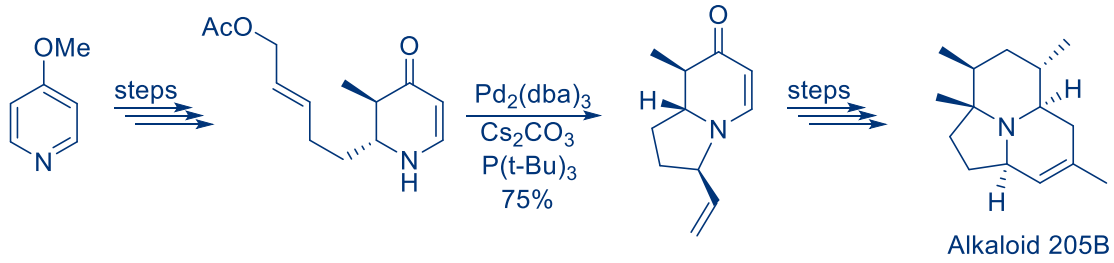
## 3.1 Introduction

The palladium-catalyzed allylation of allylic substrates, also known as the Tsuji-Trost reaction,[76-77] is one of the most synthetically useful reactions in organic synthesis.[78] The most prominent use is in the reaction of π-allyl palladium complexes with carbon nucleophiles, making it a useful method for the formation of the carbon-carbon bond. Furthermore, other heteroatom nucleophiles (such as oxygen, nitrogen, and sulphur nucleophiles) can be used in place of carbanions, expanding the scope of the Tsuji-Trost reaction even more. The wide variety of potential nucleophiles, compatible substrates and mild reaction conditions required, makes the Tsuji-Trost allylation an important step in the synthesis of various natural and pharmaceutical compounds.[79] For instance, Trost recently reported a divergent synthesis of (-)-Galanthamine, a compound used for treatment of Alzheimer's, and morphine, a widely used analgesics (**Scheme 3.1**).[80-81] One of the key steps towards the total synthesis of aforementioned compounds is a palladium catalyzed allylation of phenol nucleophile.



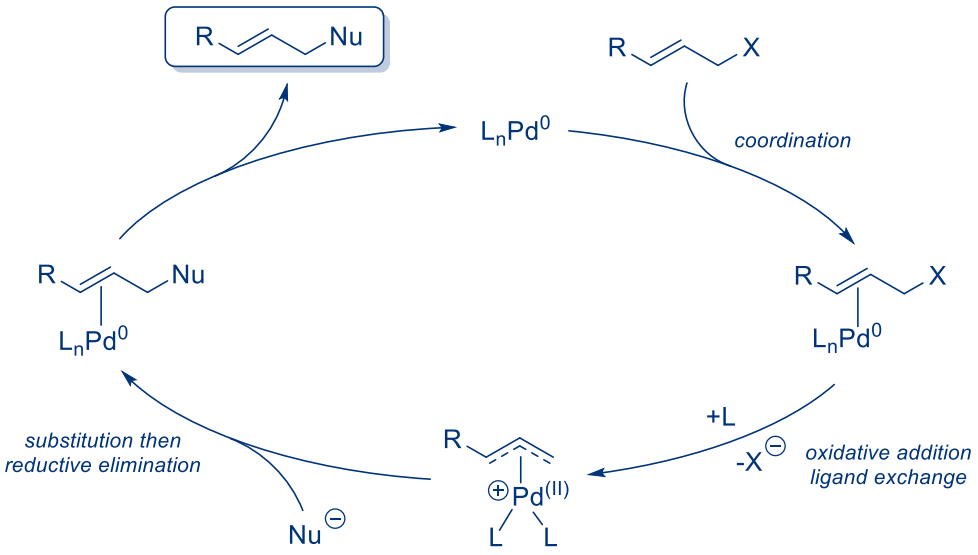

***Scheme 3.1.*** *The Tsuji-Trost reaction in the synthesis of (-)-galanthamine, codeine and morphine*

Furthermore, another application of Tsuji-Trost reaction can be found in the recently reported total synthesis of the Alkaloid 205B by Comins (**Scheme 3.2**).[82] In their 11 steps total synthesis, Tsuji-Trost reaction was used for pyrrolidine ring formation.




***Scheme 3.2.*** *The Tsuji-Trost reaction in the synthesis of alkaloid 205B.*

The mechanism of Tsuji-Trost allylation is well known and it is shown in **Scheme 3.3**.[83-84] In order to form the initial π-allyl palladium complex, the allylic moiety is often activated by means of a halide, acetate or carbonate source due to its higher reactivity.



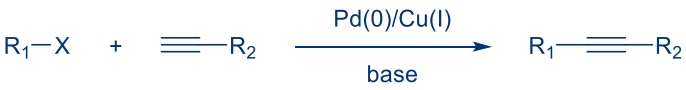

***Scheme 3.3.*** *The catalytic cycle of the Tsuji-Trost reaction*

Initially, the palladium(0) species will coordinate at the double bond of the allylic substrate, forming a $\eta^2$-allyl palladium(0) complex, followed by the attack of

palladium(0) on the C-X σ*-orbital of the leaving group, generating a cationic $\eta^3$-allyl Pd(II)$L_n$ intermediate. The nucleophile then directly attacks the $\eta^3$-allyl terminus regenerating the $\eta^2$-allyl palladium(0) complex. At the end of the reaction, the Pd(0) active species dissociates itself from the alkene and continues the catalytic cycle. The overall process features a net retention of configuration (via a double inversion pathway).[85-86] Given that the nucleophile can attack the $\eta^3$-allyl palladium complex at either position 1 or 3 of the allylic moiety, steric factors will however favor nucleophilic attack at the less-substituted terminus.[77]

### *3.1.1 Bimetallic catalysis*

Bimetallic catalysis is not a new concept in organic chemistry. In 1981, Negishi used the term bimetallic catalysis to describe zirconium and titanium catalyzed carboalumination of alkynes,[87] as well as in palladium and zinc catalyzed coupling reactions.[88] Perhaps, the most famous and synthetically useful bimetallic reaction was developed in 1975 by Sonogashira (**Scheme 3.4**).[89] Reaction uses a palladium and copper catalyst for cross-coupling of an organohalide with a terminal alkyne.



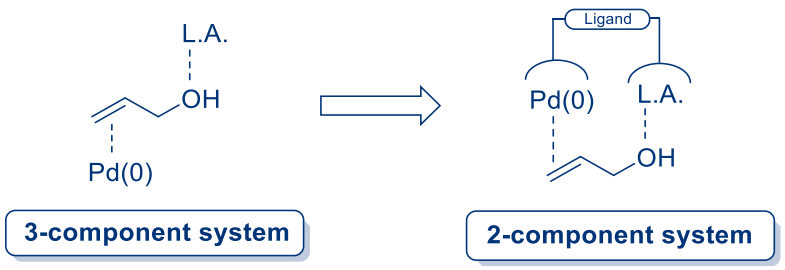

***Scheme 3.4.*** *Sonogashira reaction.*

Other bimetallic system have been developed throughout the years, such as Nozaki–Hiyama–Kishi reaction which employs nickel and chromium catalytic system.[90] Examples of bimetallic system involving d-block and f-block elements have also been reported. For instance, cerium and nickel catalyzed carbonylation of benzyl chlorides,[91] or recently reported lanthanum/silver catalytic system for asymmetric Conia-ene reactions.[92]

As already stated above, the Tsuji-Trost reaction is a good method for new bond formation, but generally requires activated allylic alcohols as substrate which leads to the generation of a stoichiometric amount of waste products.[93] For that reason, use of underivatized allylic alcohol is more acceptable as water is the only by-product, and furthermore, the derivatization step is avoided. Since the hydroxyl group is a poor leaving group, the addition of a Lewis acid is essential in order to activate the alcohol. Different water sensitive Lewis acids such as titanium isopropoxide[94-95] or titanium tetrachloride[96], as well as arsenic(III) oxide,[97] have been previously used for this purpose. However, due to the generation of water as by-product, for our research we have chosen lanthanum triflate as a stable and water tolerant Lewis acid.[33, 98]

### *3.1.2 Bifunctional ligands*

The main problem of bimetallic catalysis is that it involves a three component issue; it means that a substrate must be coordinated at the same time on both metals (3-component system), which leads to a kinetic disadvantage. This problem can be avoided by using a ligand that acts as a "bridge" between two metals, combining them into a single component (Scheme 3.5). Such catalyst and substrate thus form a 2-component system and could thereby eliminate the previously mentioned kinetic disadvantages.




***Scheme 3.5.*** *System conversion by means of a ligand; from three-component to two component system*

The designed ligand should have two binding sites with different hardness – a "soft" binding site for binding to a "soft" transition metal such as palladium or rhodium, and a "hard" binding site for binding to a "hard" lanthanides.[33, 99] This can be achieved by synthetically designing a phosphine ligand with an oxygen-containing moiety. The "soft" binding site can be provided by the phosphorus atom, and the "hard" binding site can be provided by the oxygen atom.[100-101] This methodology was then implemented in our research.

The concept of hard and soft acids and bases (HSAB theory) was introduced by Ralph Pearson in 1963 in order to explain stability of metal complexes and the mechanisms of their reactions.[102-103] Fundamentally, according to HSAB theory, "hard" species are characterized by properties such as small ionic radii, high oxidation state and low polarizability. On the other hand, "soft" species have large atomic radii, low oxidation state and are highly polarizable. The remaining borderline species possess intermediate properties. The commonly used Lewis acid and bases are presented in **Figure 3.1** according to their hardness.[104]

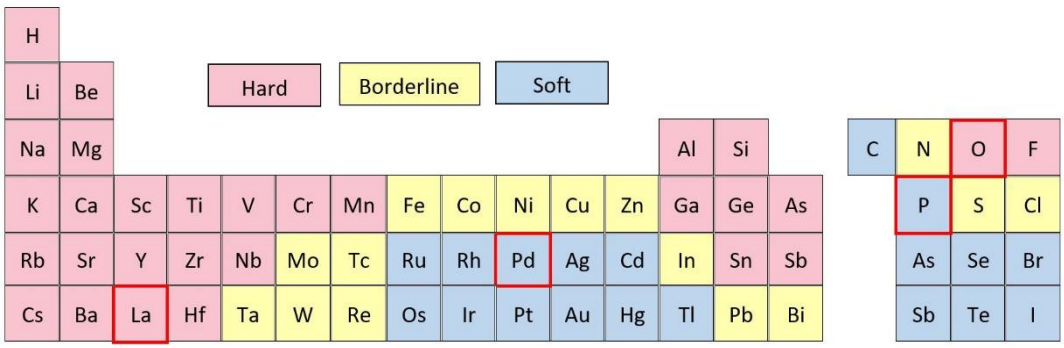



***Figure 3.1.*** *Periodic table of the elements for grouping the hard, soft and borderline acids and bases*

Several known phosphine ligands each with an oxygen-containing side chain have been synthesized previously as shown in Figure 3.2.[105]

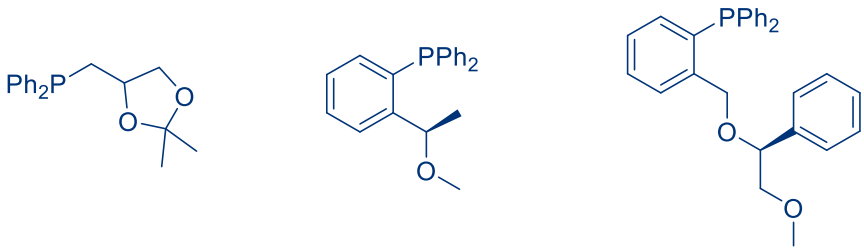



***Figure 3.2.*** *Structures of bifunctional phosphine ligands*

Phosphine ligands bearing the crown ether functionality have been synthesized and studied by Okano *et al*. in recent years (Figure 3.3).[106] Their study showed that this type of ligand act as internal phase-transfer catalysts in the palladium catalyzed cyanation of aryl halides.[107]

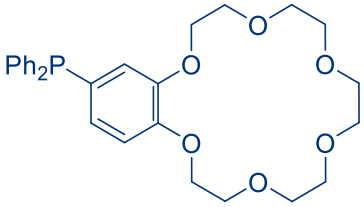



***Figure 3.3.*** *Structure of Nataro's crown ether ligand*

These aforementioned ligand types have been synthesized and employed in several studies, but were seen in little to few applications in organic syntheses.

Recently, Lim (**Figure 3.4**)[108] and Ko (**Figure 3.5**)[109] from our research group, synthesized similar phosphine ligands with the oxygen side chains installed for its use in bimetallic catalysis.

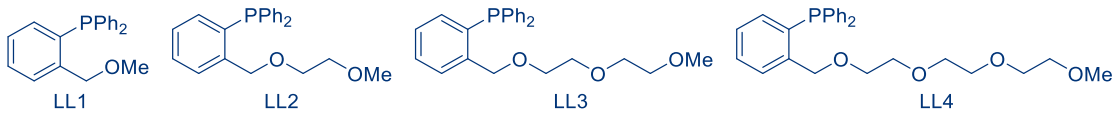



***Figure 3.4.*** *Bifunctional phosphine ligands synthesized by Lim*

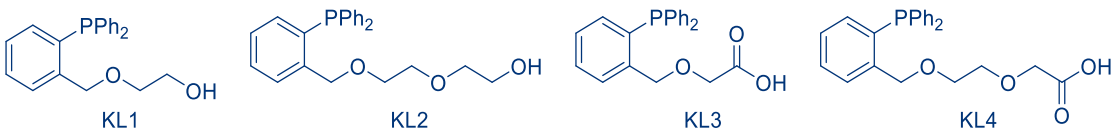
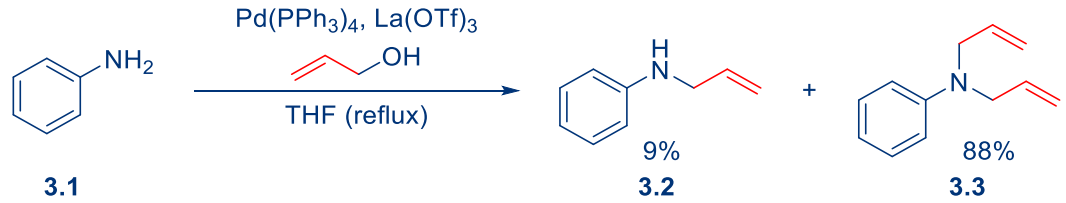



***Figure 3.5.*** *Bifunctional phosphine ligands synthesized by Ko*

Initial studies involving those ligands showed promising results, however additional studies were required.

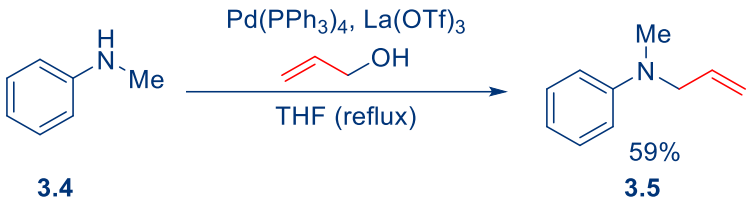
## 3.2 Results and discussion

Initial studies of bimetallic palladium-lanthanide catalysed Tsuji-Trost allylation were done by Lim, a former member of this group. Aniline (**3.1**) was chosen as the nucleophile to attack the formed $\eta^3$-allyl palladium(II) complex in the reaction and gave the desired product. The best results were achieved by using THF as a solvent at reflux, despite the likelihood that THF would compete with the allyl alcohol as a ligand for the lanthanide. The reaction did not perform well in other solvents such as $CH_2Cl_2$ and toluene, due to the low solubility of lanthanum(III) triflate in these solvents.




***Scheme 3.6.*** *Bimetallic allylation of aniline by Lim.*

Formation of both N-allylaniline (**3.2**) and N,N-diallylaniline (**3.3**) was observed even when allyl alcohol was used in a high excess (5 equivalents). The separation of the mono- and diallylated compound via flash chromatography is very challenging due to the similar $R_f$ values of both compounds (**Scheme 3.6**). The formation of both mono- and di-allylated compound has been a major drawback for aniline (**3.1**) as a substrate, hence in the work of Reich, the nitrogen nucleophile was changed to N-methylaniline (**3.4**). The resulting mono allylated product (**3.5**) obtained facilitated analysis and purification, thus allowing more accurate evaluation of our bimetallic catalytic system (**Scheme 3.7**).




***Scheme 3.7.*** *Bimetallic allylation of N-methylaniline by Reich.*

Under bimetallic conditions, the desired product was obtained in 59% yield over 20 hours. Along with the isolation of the product, starting material was recovered from the crude reaction mixture as well.

Furthermore, Reich also tested several other lanthanides, specifically neodymium, dysprosium and ytterbium, as well as scandium as a pseudo-lanthanide. However, the difference in behavior of the screened lanthanide triflates in activation of the allyl alcohol has found to be negligible. The yields were in the range of 59-63% for true lanthanides, while the yield dropped to 48% when scandium(III) triflate was used. Although scandium triflate is often known as a more potent Lewis acid than other lanthanides,[29] it appeared to be inferior to genuine lanthanide triflates in our bimetallic Tsuji-Trost allylation study. As a result of this study, lanthanum(III) triflate has been chosen as the lanthanide source.

In this work, the influence of other counterions were also examined. Cheaper sources of lanthanum(III) salts, such as chloride and acetates were selected and studied.

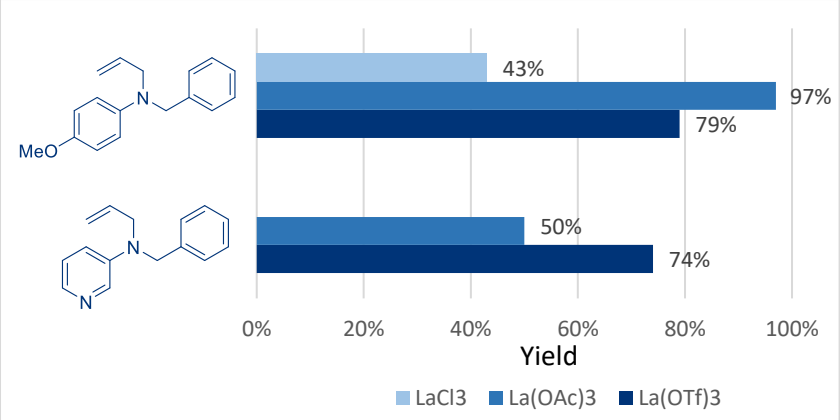



***Figure 3.6.*** *Reactivity of other lanthanum salts (Reaction conditions: substrate (1 mmol); $Pd(PPh_3)_4$ (5 mol%); $La(OTf)_3$ (10 mol%); allyl alcohol (3 eq.); dry THF (2 mL), reaction time: 20 h)*

Interestingly, both salts provided competent catalysis for selected substrates. In some cases, the reaction performed even better than the reaction with lanthanum triflate (Figure 3.6). In this reaction, it would appear that the lesser coordinating strength of the triflate ion is unimportant. Additionally, the fact that lanthanum acetate is a good activator for this reaction, provides evidence that a "hidden Brønsted acid" mechanism is not significant in this case, as *in situ* hydrolysis of lanthanum acetate would yield only a weak acid.

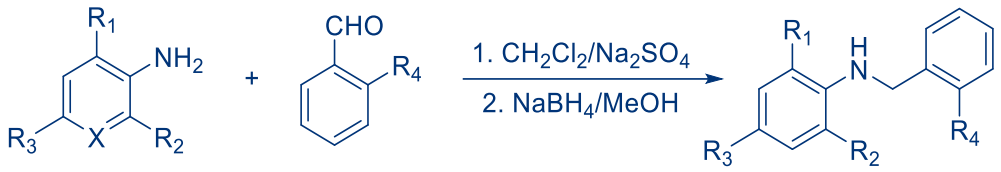
### *3.2.1 Reaction scope*

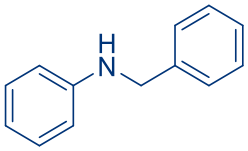
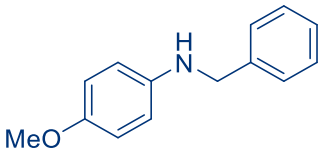
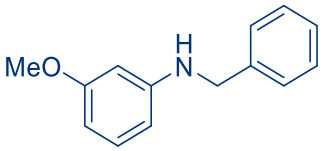
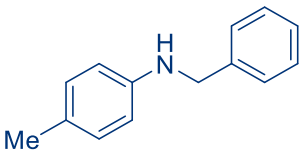
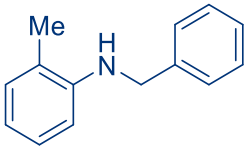
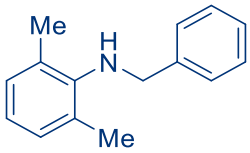
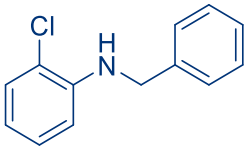
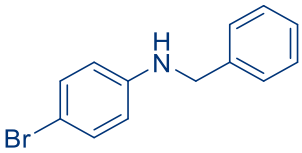
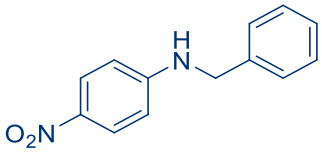
To further investigate the scope of the palladium-lanthanum co-catalyzed Tsuji-Trost reaction, we prepared a library of different monobenzylated anilines. Secondary aromatic amines were chosen for this study as they would give only mono-allylated products, enabling easier isolation of the desired product. Moreover, aromatic amines would allow us to control nucleophilic character of the nitrogen atom by simply changing substituents on the aromatic rings.

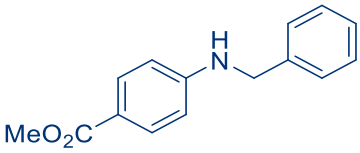
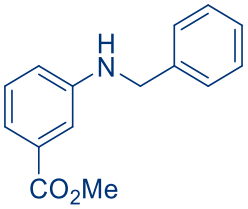
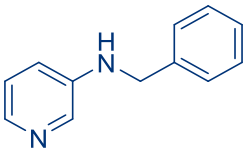
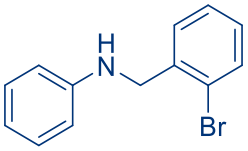
Monobenzylated amines were prepared by the condensation of benzaldehyde with aromatic anilines to give the corresponding substituted imine. The imine was

subsequently reduced with sodium borohydride to afford desired N-benzylated aniline in fair to good yields (**Table 3.1**).

***Table 3.1.*** *Monobenzylation of anilines*

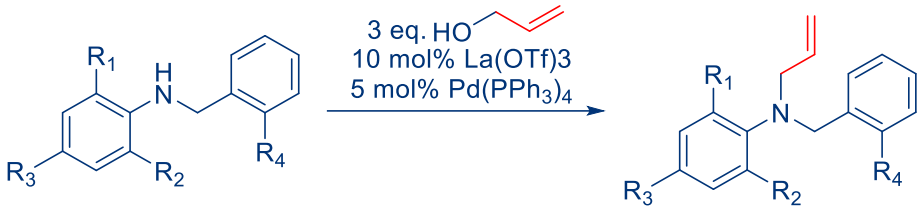


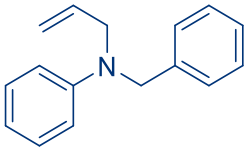
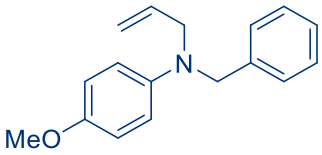
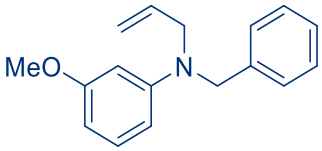
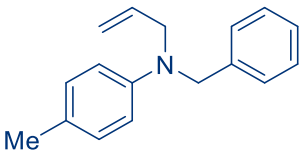
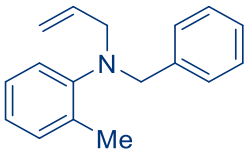
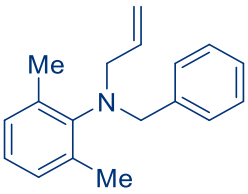
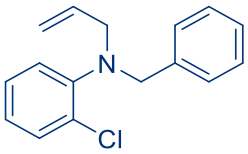
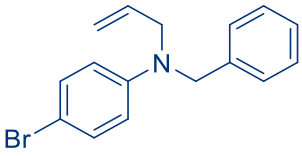
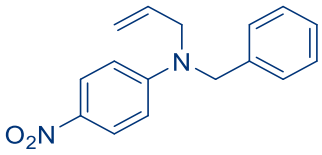

| Entry | Product | Yield (%) | Compound |
|---|---|---|---|
| 1 |  | 86 | **3.6** |
| 2 |  | 85 | **3.7** |
| 3 |  | 91 | **3.8** |
| 4 |  | 67 | **3.9** |
| 5 |  | 69 | **3.10** |
| 6 |  | 54 | **3.11** |
| 7 |  | 52 | **3.12** |
| 8 |  | 76 | **3.13** |
| 9 |  | 68 | **3.14** |

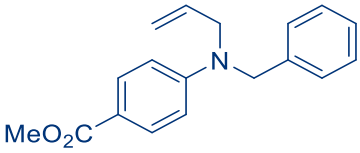
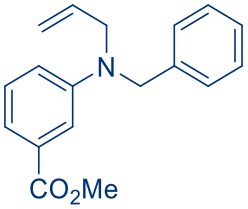
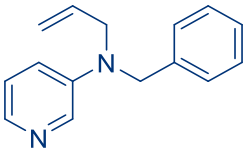
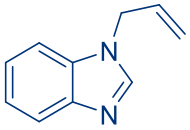
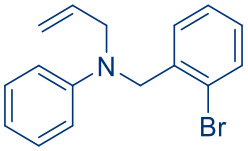
| | | | |
|---|---|---|---|
| 10 |  | 57 | **3.15** |
| 11 |  | 30 | **3.16** |
| 12 |  | 65 | **3.17** |
| 13 |  | 72 | **3.18** |

With the desired anilines at hand, we could approach to attempt bimetallic Tsuji-Trost allylation reaction using following standard reaction setup. The reactions were carried out in dry THF under reflux and inert atmosphere for 20 h. As palladium(0) source, tetrakis(triphenylphosphine) palladium(0) was used in an amount of 5 mol%. Lanthanum triflate was chosen as the Lewis acid and it was used in catalytic amount of 10 mol%. For the electrophile, allyl alcohol was chosen as the substrate since it was structurally simple and without regioselectivity issues. The results of bimetallic Tsuji-Trost allylation are presented in **Table 3.2**.

***Table 3.2.*** *Allylation of N-substituted anilines*




| Entry | Product | Yield (%) | Compound |
|---|---|---|---|
| 1 |  | 75 | **3.19** |
| 2 |  | 79 | **3.20** |
| 3 |  | 61 | **3.21** |
| 4 |  | 56 | **3.22** |
| 5 |  | 13 | **3.23** |
| 6 |  | 6 | **3.24** |
| 7 |  | 16 | **3.25** |
| 8 |  | 11 | **3.26** |
| 9 |  | 0 | **3.27** |

| | | | |
|---|---|---|---|
| 10 |  | 0 | **3.28** |
| 11 |  | trace | **3.29** |
| 12 |  | 74 | **3.30** |
| 13 |  | 95 | **3.31** |
| 14 |  | 21 | **3.32** |

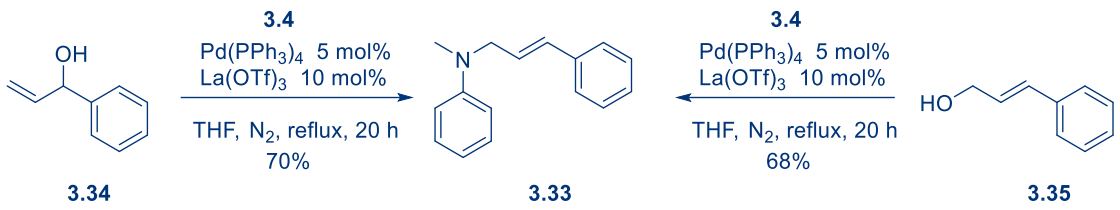
Reaction conditions: substrate (1 mmol); $Pd(PPh_3)_4$ (5 mol%); $La(OTf)_3$ (10 mol%); allyl alcohol (3 eq.); dry THF (2 mL).

As mentioned before, the allylation of N-methylaniline (**3.4**), yielded 59% of N-allyl-N-methylaniline (**3.5**). Compared to the results above, allylation of **3.6** yielded product **3.19** (Table 3.2, Entry 1) in a much better yield of 75%. The benzyl group attached directly to nitrogen atom, was evidentially a better activating group than the methyl group, thereby enhancing nucleophilic character of the nitrogen atom, attributing to the higher yield. Introducing an methoxy (-OMe) additional activating group in the *para* position of aniline generates an even better nucleophile overall, resulting in an easier attack on the Pd(II) $\eta^3$-allylic complex, which would explain the high yield of product **3.20** (Table 3.2, Entry 2). A similar effect was observed when a methoxy or methyl group was in the *para* or *meta* position (**Table 3.2**, Entry 3 and 4). On the contrary, when a strongly (-$NO_2$, compound **3.27**) or moderately (-$CO_2$Me, compound **3.28**) deactivating group was attached on the ring in *para* position to nitrogen, the reaction gave no product as expected (Table 3.2, Entry 9 and 10). When the aromatic system

contains a weakly deactivating group, such as halogen atom, we observed formation of allylated product but in poor yields. In particular, halogen atoms in compound **3.12** and **3.13** with relatively strong electron withdrawing inductive effects generated poor nucleophiles and eventually resulted in poor yields of compound **3.25** and **3.26** (Table 3.2, Entry 7 and 8). Since the inductive effect is dependent on distance, a slightly higher yield was observed for compound **3.32** (Table 3.2, Entry 14), where the bromine atom was attached in *ortho* position on the benzyl group. Furthermore, poor yields were also observed when the nucleophilic nitrogen atom was sterically hindered by bulky methyl groups such as in compounds **3.23** and **3.24** (Table 3.2, Entry 5 and 6). In one interesting case, the pyridine containing substrate (**3.17**) underwent bimetallic Tsuji-Trost allylation satisfactory. Although we expected interactions of the pyridine nitrogen atom with the Lewis acid, we observed only formation of allylated product **3.30** in good yield (Table 3.2, Entry 12). Therefore, we postulated that the lanthanum ion is able to coordinate to the pyridine nitrogen and still have room for coordination to the allyl alcohol in the reaction. This result demonstrates that the reaction is genuinely metal-catalyzed, and a "hidden Brønsted acid" pathway is unlikely to be significant.

To our delight, one of the best substrates for our bimetallic Tsuji-Trost allylation study was benzimidazole, since N-allylbenzimidazole (**Table 3.2**, Entry 13) was formed in very high yield.

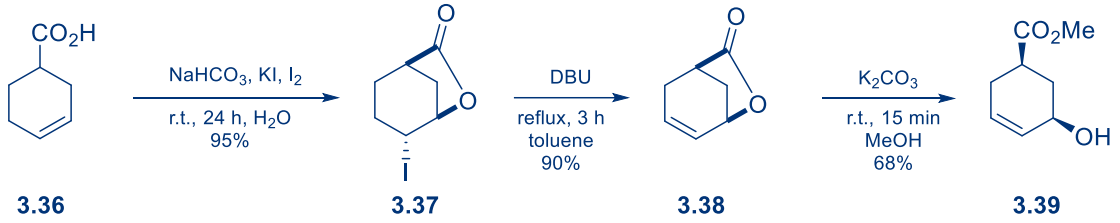
Studies on the regioselectivity of the Pd-La bimetallic catalysis were studied by Reich, and the observed regioselectivity is consistent with the generally accepted mechanism for the Tsuji-Trost allylation. Cinnamyl alcohol and its isomer, 1-phenylprop-2-en-1-ol, gave the same product in almost identical yields (**Scheme 3.8**).




***Scheme 3.8.*** *Bimetallic allylation of Cinnamyl alcohol and 1-phenylprop-2-en-1-ol*

### *3.2.2 Stereoselectivity of the bimetallic Tsuji-Trost allylation*

To investigate stereoselectivity of the palladium-lanthanide co-catalyzed Tsuji-Trost reaction, the chiral cyclohexanol **3.39** was synthesized (**Scheme 3.9**).

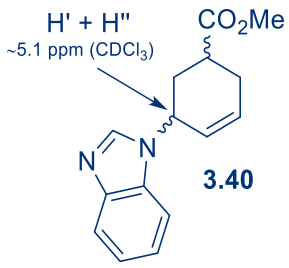



***Scheme 3.9.*** *Synthesis of cis-3-hydroxycyclohex-4-en-1-carboxylic acid methyl ester*

Following reported procedure[110], the starting material, 3-cyclohexene-1-carboxylic acid (**3.36**) was first subjected to iodolactonisation to form the iodolactone **3.37** in 95% yield, followed by elimination of the iodo-substituent with DBU generating olefin **3.38** in 90% yield. Under basic conditions in methanol, the lactone ring was opened to afford the desired *cis*-methyl ester **3.39** in 68% yield.

Later, compound **3.39** was subjected to the bimetallic reaction conditions with benzimidazole, and product **3.40** was obtained in 91% yield as an inseparable 1.7:1 ratio of isomers. The *cis* or *trans* relationship between the benzimidazole and ester substituents on the cyclohexene ring was used to determine if the substrate underwent inversion or retention in the model reaction. However, the proton signal at the

stereogenic center that could help us determine and distinguish between the major and minor isomer, appeared as an overlapped signal at 5.1 ppm in $CDCl_3$.




Hence, we looked into traditional NMR techniques which could help us to distinguish proton signals of our interest. Solvent effect have been well studied in NMR spectroscopy.[111-112] Due to its "disk" like shape and large diamagnetic anisotropy, it is known that aromatic solvents ($C_6D_6$) tend to produce high-field shifts of the solute protons.[113]

Indeed, when our NMR solvent was changed to deuterated benzene ($C_6D_6$), a high-field shift was observed and gratifyingly the proton signal of our interest (H' and H") became two separate multiplets in the $^1H$ NMR. The multiplet at 4.2 ppm corresponds to minor isomer, while the multiplet at 4.35 ppm corresponds to the major isomer (**Figure 3.7**).

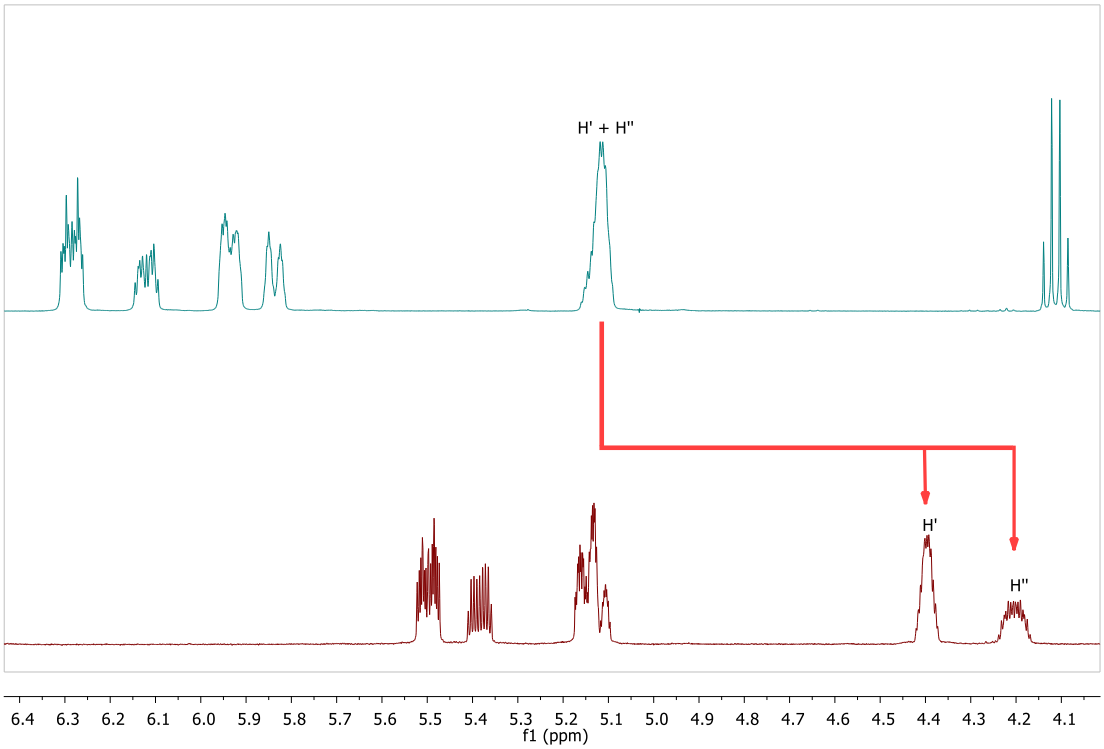
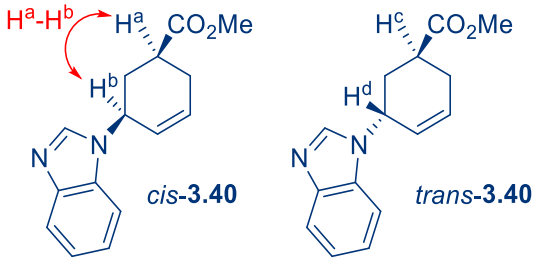



***Figure 3.7.*** *Solvent effect on chemical shift of compound (green – $^1$H NMR of **3.40** in $CDCl_3$; red – $^1$H NMR of **3.40** in $C_6D_6$)*

The determination of the stereoselectivity was performed by means of 2D $^1$H-$^1$H NOESY NMR spectroscopy (**Figure 3.8**). Cross peak relating to $H^a$-$H^b$ interactions revealed that the signals of the major product corresponded to the *cis*-isomer. Additionally, the lack of NOE interactions between $H^c$ and $H^d$ (minor product) suggests that the minor product is the *trans*-isomer.



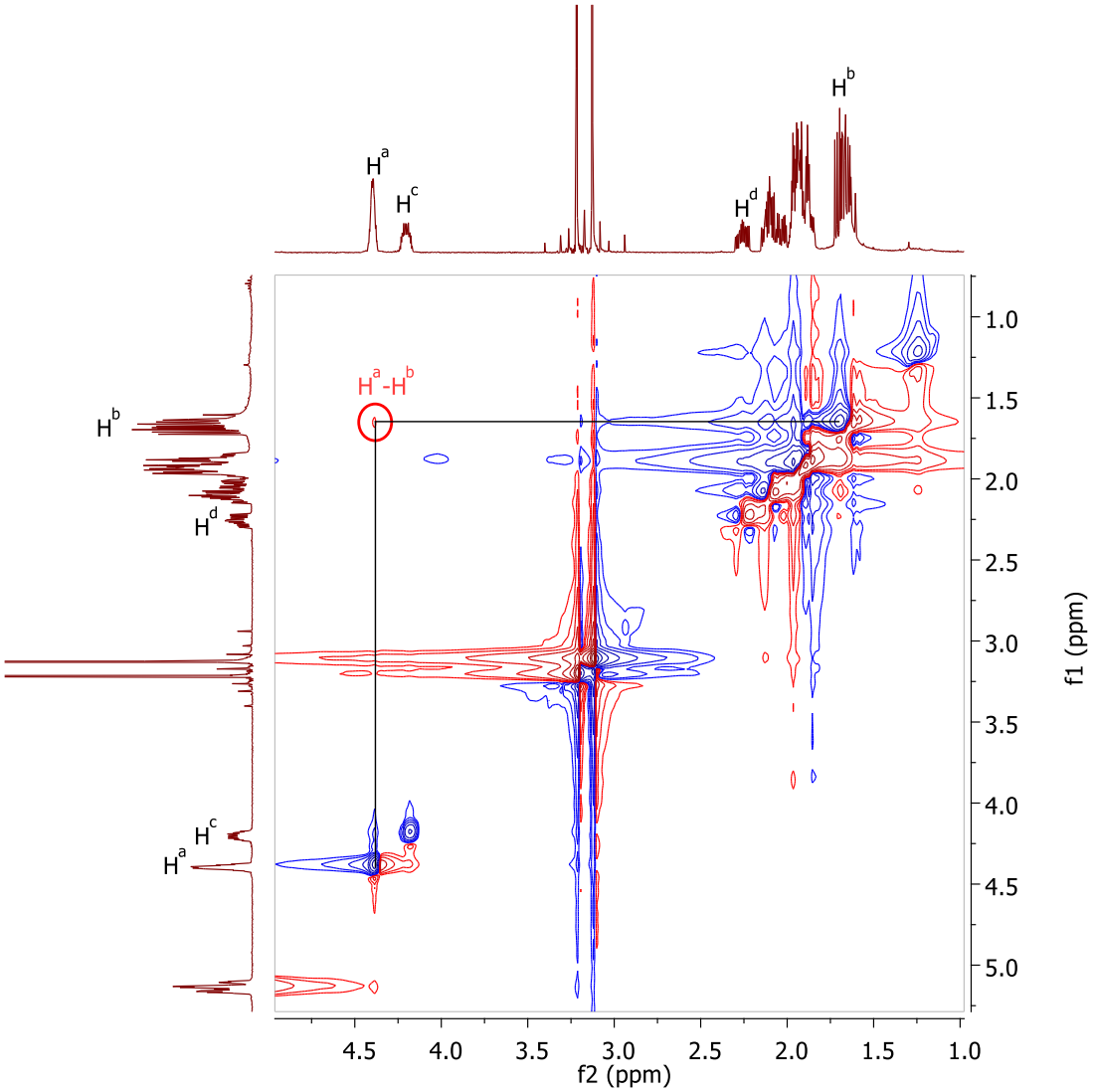
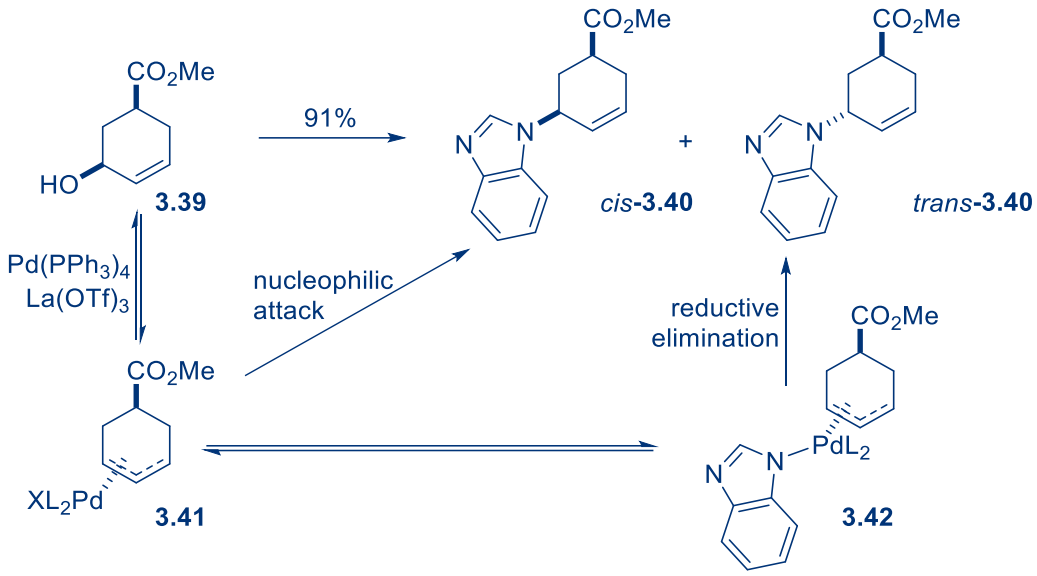



***Figure 3.8.*** *2D 1H-1H NOESY NMR spectrum of* ***3.40***

The *cis*-isomer (*cis*-**3.40**) corresponds as a result of the traditional Tsuji-Trost double inversion mechanism pathway (**Scheme 3.10**) . Likewise, Kimura *at al.* observed a similar result by using triethyl borane as the activator.[114-115] To test the stability of cyclohexanol substrate **3.39** under the bimetallic reaction conditions, the compound was subjected to the standard reaction conditions. After 20 hours, compound **3.39** was successfully recovered, suggesting that it is stable and does not undergo epimerization under the bimetallic conditions. Therefore, we concur with Kimura's suggestion that C-N bond formation proceeds by both straightforward nucleophilic attack on intermediate **3.41** (resulting in net retention of configuration) and by a Pd-

coordination-reductive elimination pathway via Pd-allyl complex **3.42**, resulting in overall inversion of configuration to give the *trans* isomer (**Scheme 3.10**).




***Scheme 3.10.*** *Stereochemical test*

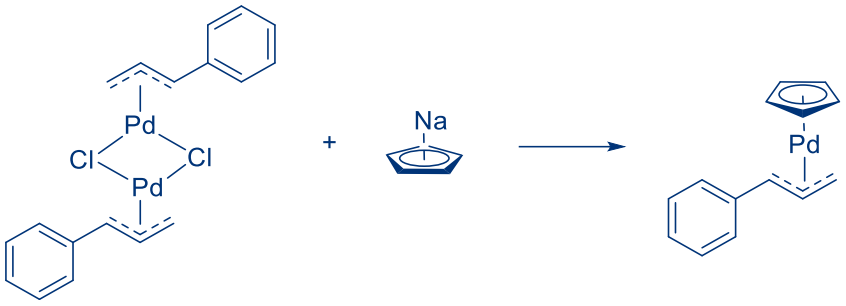
An additional experiment was also performed using lanthanum(III) acetate, which increased the *cis*/*trans* ratio to 6.25:1, however in slightly lower yield of 72%.

### *3.2.3 Influence of bifunctional ligands*

As mentioned before, a series of bifunctional phosphine ligands have been synthesized in our group.[108-109] Several ligands have been studied so far in bimetallic Tsuji-Trost allylation and have shown a promising approach towards enhancing the activity of the palladium-lanthanum co-catalytic system.[108] However, a weakness of this established system is in the reproducibility of the results.

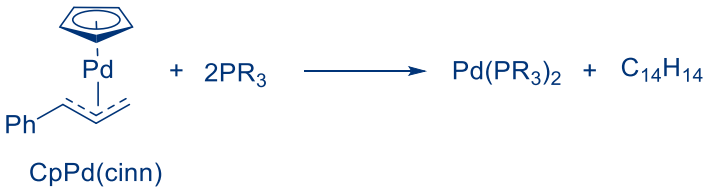
Specifically, when bifunctional phosphine ligands were used in bimetallic Tsuji-Trost reaction, the source of Pd(0) was changed to $Pd_2(dba)_3CHCl_3$, since it does not contain phosphine ligands of its own that could possibly interfere with the bifunctional ligands. However, it is known that $Pd_2(dba)_3CHCl_3$ often comes accompanied with impurities and therefore impacts the outcome and reproducibility of

the reaction.[116] Later on, cyclopentadienyl (π-cinnamyl) palladium(II), ($\eta^3$-1-$PhC_3H_4$)($\eta^5$-$C_5H_5$), came to our attention as an alternative to $Pd_2(dba)_3CHCl_3$.[117-118]




***Scheme 3.11.*** *Preparation of cyclopentadienyl (π-cinnamyl) palladium(II) catalyst*

This Pd(II) compound is a precursor for an actual Pd(0) catalyst and possesses several advantages, such as easy preparation (**Scheme 3.11**), handling and moreover, it is easily converted to an actual Pd(0) catalytic species by gentle heating in the presence of the phosphine ligand (**Scheme 3.12**).




***Scheme 3.12.*** *Reduction of Pd(II) to Pd(0)*

In this study, cyclopentadienyl (π-cinnamyl) palladium(II) was used to test the performance of *N*-methylaniline (**3.4**) in the ligand mediated bimetallic Tsuji-Trost allylation. For that purpose, we used several ligands prepared in our group, as shown in **Figure 3.9**. The synthesis of the ligand **3.52** will be discussed later in this chapter.

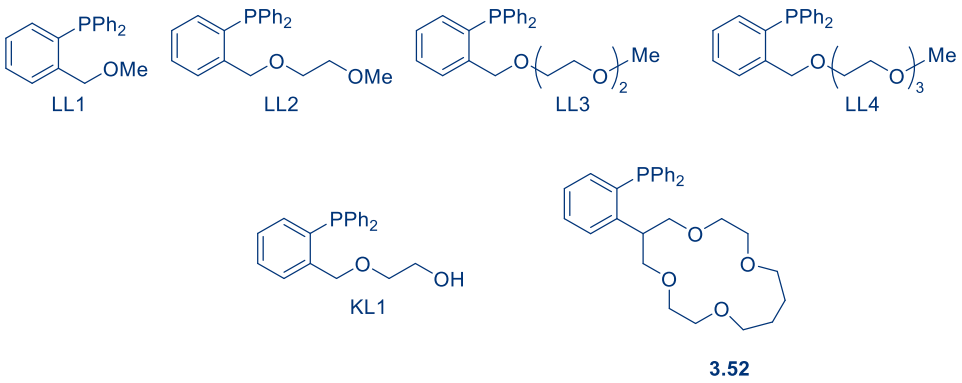
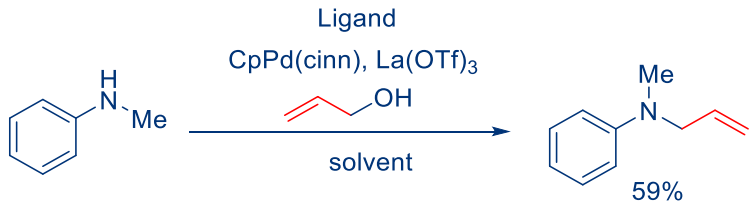



***Figure 3.9**. Bifunctional phosphine ligands used in this study*

To begin with, the model reaction of allyl alcohol with **3.4** was conducted in the presence of triphenylphosphine ($PPh_3$). The product **3.5** was obtained in 65% yield over the 5.5 hours (**Table 3.3**, Entry 1). Setting this as a control reaction, we investigated reactions with other bifunctional ligands.

***Table 3.3.** Influence of bifunctional phosphine ligands*




**3.4** **3.5**

| Entry | Temp/°C | Solvent | Ligand | Reaction time | Yield / % |
|---|---|---|---|---|---|
| 1 | 50 | THF | $PPh_3$ | 5.5 | 65 |
| 2 | 40 | THF | **LL1** | 3.5 | 79 |
| 3 | 50 | THF | **LL1** | 2 | 82 |
| 4 | r.t. | THF | **LL2** | 12 | 73 |
| 5 | 40 | THF | **LL2** | 2.5 | 72 |
| 6 | 50 | THF | **LL2** | 2 | 89 |
| 7 | 50 | THF | **LL3** | 3.5 | 75 |
| 8 | 50 | THF | **LL4** | 8 | 71 |
| 9 | 50 | THF | **KL1** | 6 | 86 |
| 10 | 50 | THF | **3.52** | 6 | 58 |
| 11 | 50 | toluene | **LL2** | 3 | 83 |
| 12 | 50 | toluene | **LL4** | 3 | 79 |
| 13 | 50 | toluene | **3.52** | 3 | 77 |

Reaction conditions: substrate (1 mmol); CpPd(cinn) (5 mol%); $La(OTf)_3$ (10 mol%); ligand (10 mol%); allyl alcohol (3 eq.); dry THF (2 mL);

The reaction of allyl alcohol with N-methyl aniline (**3.4**) and employment of ligand **LL1** yielded 79% allylation product at 40 °C over 3.5 hours. Increasing temperature to 50 °C resulted with a slightly higher yield (82%) and full conversion after 2 hours. Similar results were observed with ligand **LL2** and **LL3**, and realized that the reaction is much slower at room temperature, and full conversion was observed only after 12 hours. When ligands **LL4**, **KL1** and **3.52** were employed, allylation product was observed in comparable yields, however the reaction time needed for full conversion was significantly longer.

The solvent effect on ligand mediated bimetallic catalysis has been investigated as well. For this purpose, ligands **LL2**, **LL4** and **3.52** have been chosen and reactions were performed in toluene (**Table 3.3**, Entries 11, 12, 13).

Since toluene is non-coordinating solvent, only the ligand will coordinate to Lewis acid, whereas in THF ligand has to compete with the solvent itself. More oxygen atoms ligand contains, means more possible binding sites to Lewis acid. In the case of **LL4** and **3.52** four available oxygen atoms coordinate to Lewis acid forming a very stable catalytic system, and thus results with increased yield and faster reaction time.

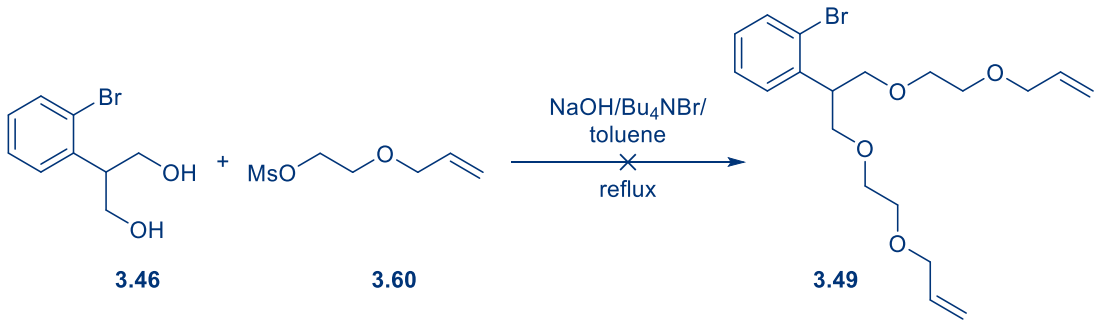
Although a general trend cannot be observed, these results clearly indicate that the use of bifunctional ligands in the reaction improves overall efficiency of the catalytic system by overcoming the inherent kinetic disadvantage of the three-component system.

### *3.2.4 Synthesis of the bifunctional crown ether ligand*

Our goal in this research is also to create an adequate library of bifunctional ligands which we will use in our research. As stated before, in our previous work we

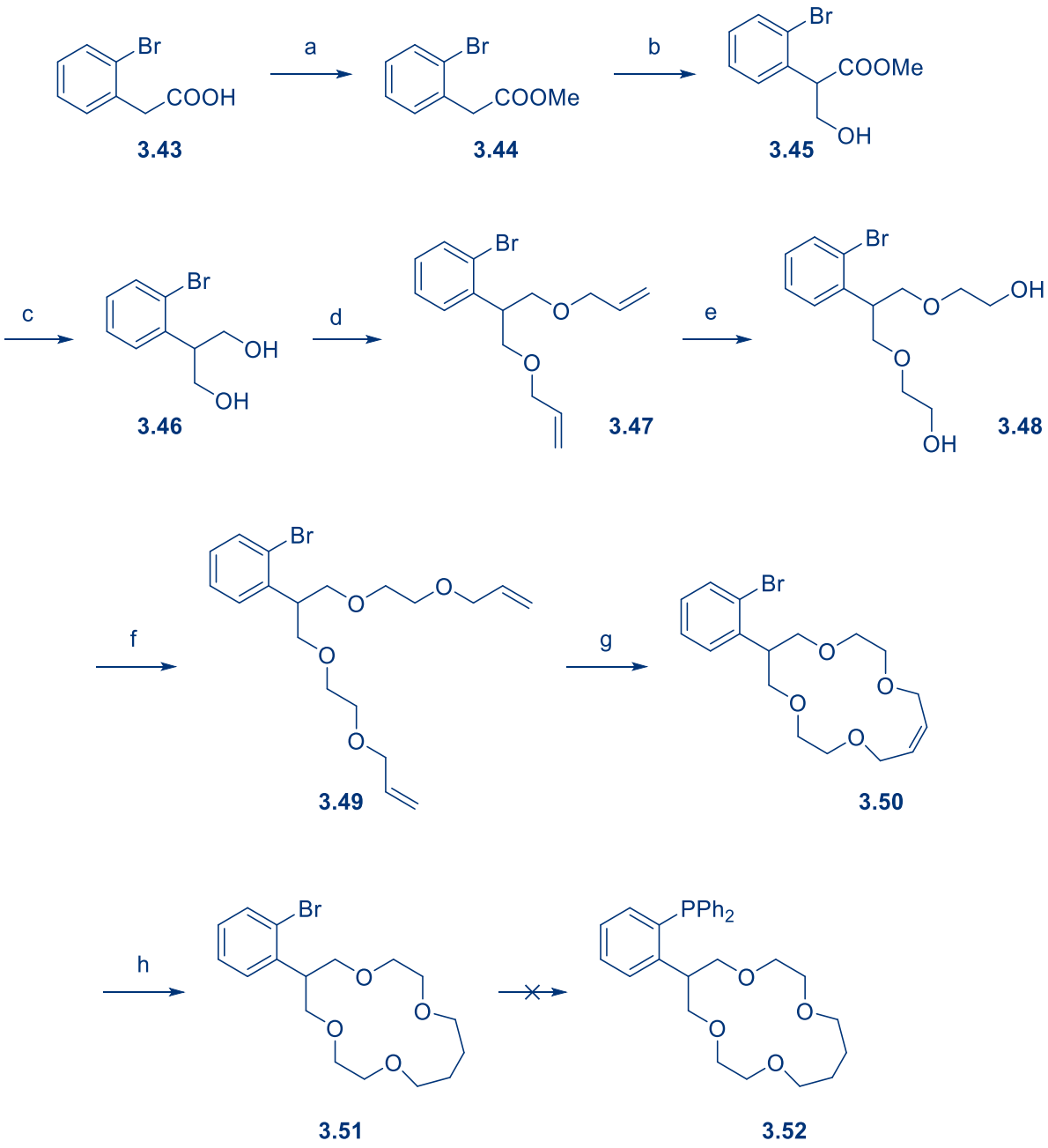
synthesized different phosphine ligands with the oligoether side-chain. Moving forward, we have made progress in synthesizing bifunctional phosphine ligand which contains the crown ether moiety. Our initial synthetic route is shown on **Scheme 3.14**.

Beginning with readily available 2-bromophenylacetic acid **3.43**, using well established experimental procedure,[119] we prepared methyl ester **3.44** in quantitative yield. Subsequently, ester **3.44** in basic conditions underwent nucleophilic addition with formaldehyde formed *in situ* from paraformaldehyde. Product **3.45** was afforded in excellent yield. Following reduction of ester **3.45** with $LiAlH_4$ at room temperature gave desired diol **3.46**. The desired product **3.49** was not observed, when an alternate shorter pathway was used (**Scheme 3.13**). This is probably due to ether oxygen atom in compound **3.60** which make this compound a poor substrate for the $S_N2$ reaction.




***Scheme 3.13.*** *Failed synthesis of* ***3.49***

Hence, we changed our strategy by using allyl bromide as substrate for Williamson ether synthesis,[120] affording product **3.47** in good yield. Branched allyl ether **3.47** was treated with ozone at 0 °C, and after reductive work-up with $NaBH_4$, a branched diol **3.48** was afforded in good yield. The side-chains of **3.48** were prolonged one more time with allyl bromide using the same procedure for modified Williamson ether synthesis, affording branched allyl-oligoether **3.49**.

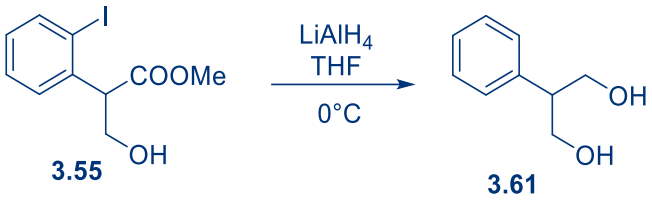



***Scheme 3.14.*** *a. MeOH, HCl, 98%; b. paraformaldehyde, NaOMe, 91%; c. $LiAlH_4$, 86%; d. allyl bromide, NaOH, $Bu_4N^+Br^-$, 88%; e. 1. $O_3$, 2. $NaBH_4$, 78%; f. allyl bromide, NaOH, $Bu_4N^+Br^-$, 60%; g. Grubbs' II catalyst, 45%; h. Wilkinson's catalyst, $H_2$, 89%.*

The next step in our synthesis was the ring closing metathesis (RCM) of oligoether **3.49** using Grubbs' second-generation catalyst in amount of 5 mol%. To avoid side-reaction, dimerization or polymerization, our substrate **3.49** was highly diluted in $CH_2Cl_2$.[121-122] In order to extend catalyst activity, we add the catalyst

portion-wise in 30 min intervals over 2 h. At the whole time nitrogen gas was bubbled through the reaction mixture in order to remove ethene, which usually promotes catalyst decomposition.[123] In the RCM step, a lower yield of **3.50** was observed (45%) which is probably due to the large ring size.[124] We also tried Grubbs' first generation catalyst for RCM step, but the observed yield was slightly lower than in RCM with Grubbs' II (41%). Given that the substrate **3.50** contains an aryl bromide, we had to use Wilkinson's catalyst [$RhCl(PPh_3)_3$] as catalyst for the hydrogenation since this catalyst displays the desired selectivity.[125] The desired saturated product **3.51** was afforded in good yield (89%). The last step in our synthesis was the palladium catalyzed cross-coupling phosphination reaction with diphenylphosphine. We applied the same, well established reaction conditions as we used for cross-coupling of previously developed ligands in our group.[108] However, using $Pd(PPh_3)_4$ and triethylamine in toluene under inert atmosphere and at reflux, no product was observed after 24 hours, and only starting material **3.51** was recovered. This is possibly due to the lesser reactivity of aryl bromides and chlorides than the corresponding aryl iodide.[126] Other catalysts, such as $Pd_2(dba)_3CHCl_3$, $Pd(OAc)_2$ and $PdCl_2(PPh_3)_2$ were unsuccessfully tested as well.

Our next step was to start the entire synthesis from beginning with the corresponding aryl iodide (**3.53**). Following previously established reaction conditions, methyl ester **3.54** was obtained in quantitative yield. Subsequently, compound **3.55** was prepared by the aldol reaction in quantitative yield. However, it was observed that the aryl iodide was lost after reducing compound **3.55** using $LiAlH_4$ (**Scheme 3.15**, **Figure 3.10**).




***Scheme 3.15.*** *Reduction of* ***3.55***

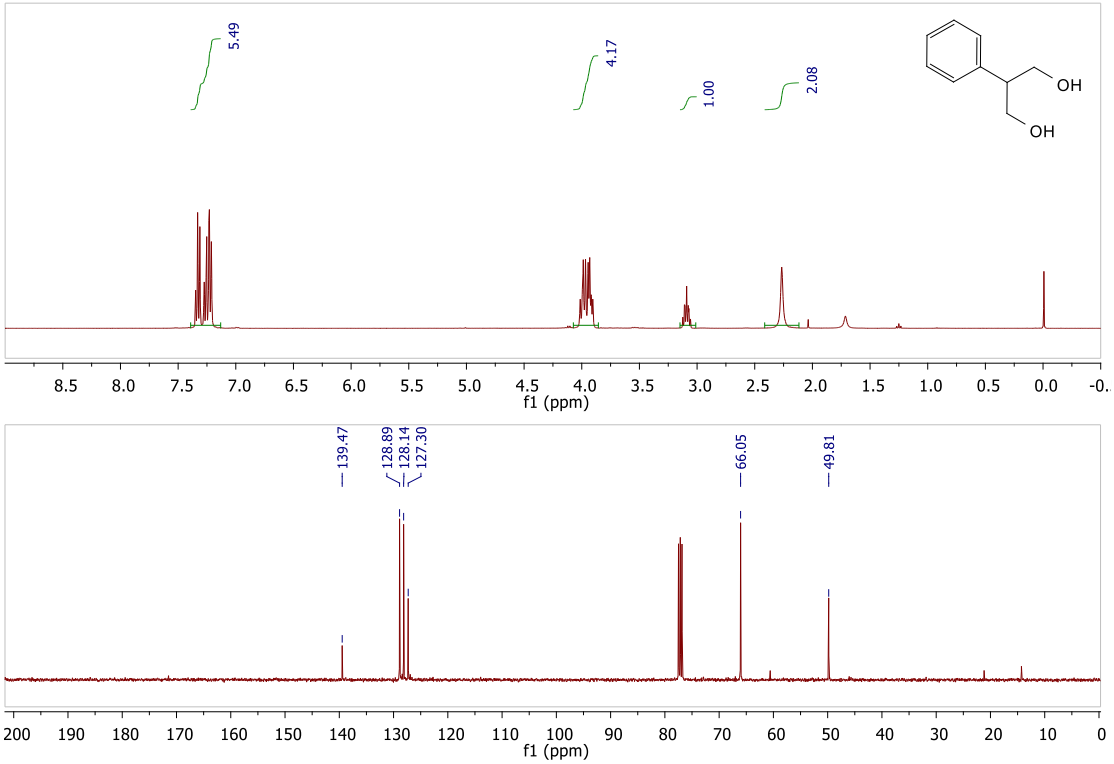



***Figure 3.10.*** *$^{1}H$ NMR and $^{13}C$ NMR of compound 3.61*

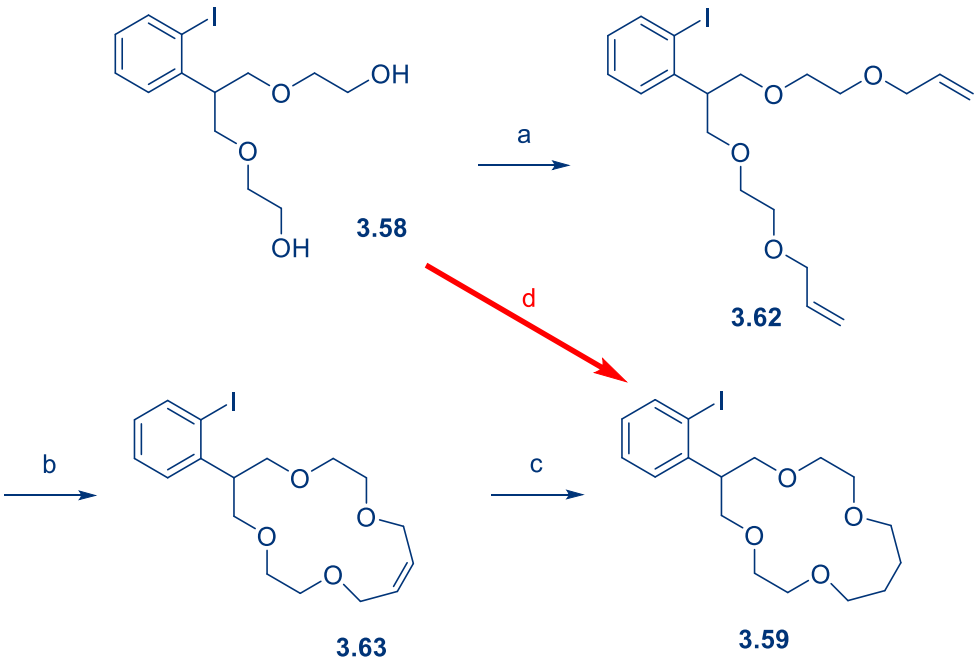
Hence, $NaBH_4$ was used instead even though it was not a commonly used reagent for the ester reduction, and the desired diol **3.56** was afforded in 85% yield. Williamson ether synthesis was then used to prepared branched ether **3.57**. Compound **3.57** was afforded in a good yield of 77% only when NaH was employed as a base, whereas use of NaOH afforded only 41%. Ozonolysis of compound **3.57**, followed by $NaBH_4$ reduction of the generated ozonide provided the desired diol **3.58** in a high yield of 90%. Once again, following the previously established synthetic route, we tried to prepare the branched alkene **3.62** by Williamson ether synthesis. However, this time reasonable yields of the desired branched alkene **3.63** could not be achieved and only

15% product was isolated accompanied by the starting material. Nevertheless, the isolated product was used in the RCM step with Grubbs' II catalyst. Unfortunately, the anticipated cyclized product was obtained in a disappointing yield of 18%. Other catalysts were tested as well, but to no improvement as shown in **Table 3.4**

***Table 3.4.*** *Results for ring closing methatesis of* ***3.64***

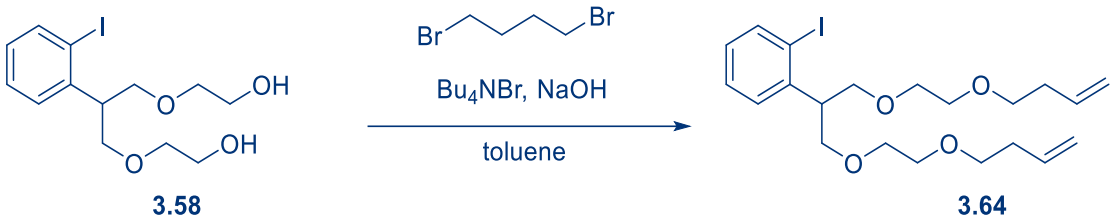
| Entry | Catalyst | Time / h | Yield / % |
|---|---|---|---|
| 1 | Grubbs I | 4 | 11 |
| 2 | Grubbs II | 6 | 18 |
| 3 | Hoveyda-Grubbs II | 20 | 14 |

Unsatisfied with the results from previous two steps, we decided to change the synthetic scheme and form the 15-membered ring using 1,4-dibromobutane with diol **3.58** in the Williamson ether synthesis as shown in **Scheme 3.16**.




***Scheme 3.16.*** *Alternate route to* ***3.59****; a. allyl bromide, NaOH,* $Bu_4N^+Br^-$*, b. RCM, c. Wilkinson's catalyst,* $H_2$*, d. 1,4-dibromobutane, NaOH,* $Bu_4N^+Br$*, 44%*

When toluene was used as a solvent for this reaction, an unwanted elimination happened (**Scheme 3.17**), forming the branched alkene as the major product accompanied with starting material.



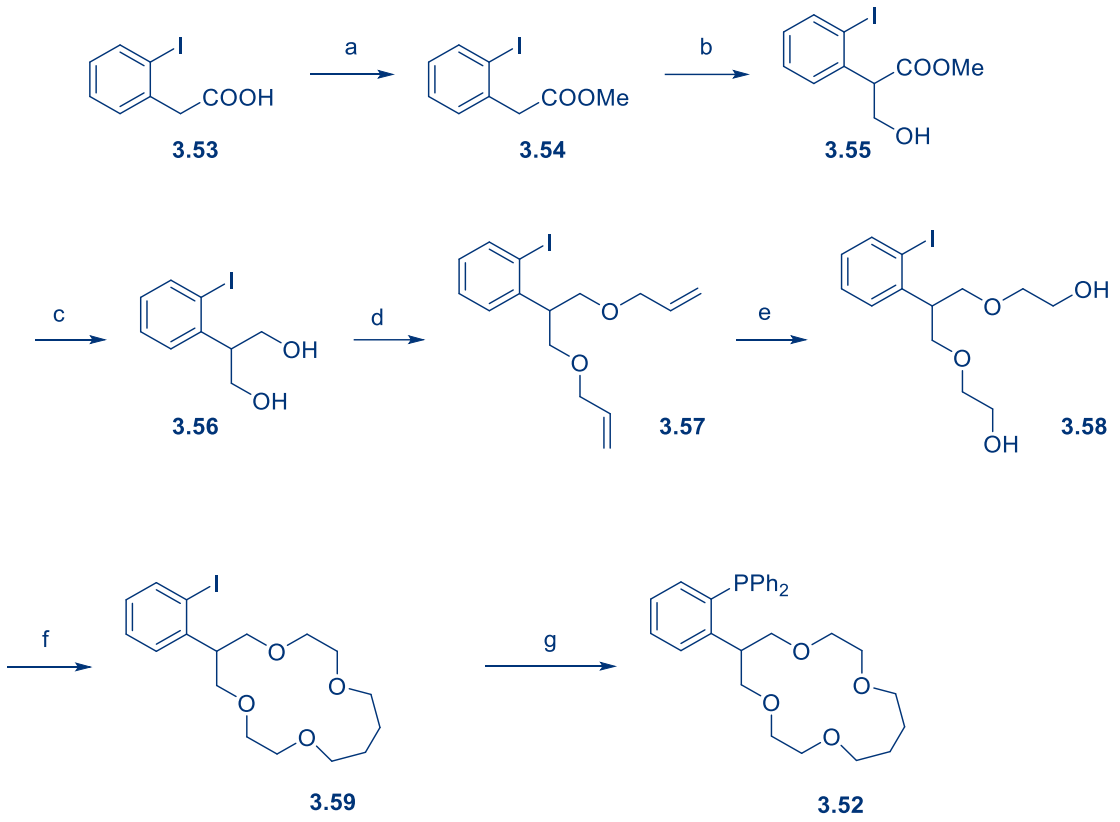

**3.58** **3.64**

***Scheme 3.17.*** *Formation of the side product 3.64.*

Luckily, change of solvent to THF yielded the desired pseudo-crown ether ring containing compound **3.59** with 44%.

Our first attempt of the cross-coupling phosphination reaction failed when $Pd(PPh_3)_4$ was used as a catalyst. Fortunately, the desired difunctional phosphine ligand **3.52** was successfully synthesized in 51% yield when the catalyst was changed to cyclopentadienyl (π-cinnamyl) palladium(II). Ligand **3.52** was obtained as a colorless oil and it was characterized by $^{1}H$ and $^{13}C$ NMR as well as $^{31}P$ NMR spectroscopy showing a characteristic phosphine peak at -15.51 ppm.

In summary, pseudo-crown ether containing phosphine ligand **3.52** was successfully synthesized over seven steps in an overall yield of 13%.




***Scheme 3.18.*** *a. MeOH, HCl, quantitative yield; b. paraformaldehyde, NaOMe, quantitative yield; c. $NaBH_4$, 85%; d. allyl bromide, NaH, $Bu_4N^+Br^-$, 77%; e. 1. $O_3$, 2. $NaBH_4$, 90%; f. 1,4-dibromobutane, NaOH, $Bu_4N^+Br$, 44%; g. Pd(cinnamyl)Cp, $Et_3N$, $PHPh_2$, 51%*

## 3.3 Conclusion and future work

In this chapter, we have shown an interesting catalytic synergy of d-block and f-block elements. Palladium-lanthanide co-catalyzed Tsuji-Trost allylation has been shown to be an efficient and powerful synthetic tool, where lanthanides act as a co-catalyst to activate the allylic alcohol and palladium acts as an actual transition metal catalyst. With several experiments, we have shown that the reaction is catalyzed with genuine Lewis acid, and a "hidden Brønsted acid" mechanism is unlikely to be significant. Interestingly, less expensive lanthanide chlorides and acetates can be used as Lewis acids. Electron richer secondary aromatic anilines are usually the best substrates for this reaction. Furthermore, pseudo-crown ether phosphine ligand (**3.52**) has been successfully synthesized. Besides, various bifunctional phosphine ligands that are able to coordinate to both palladium and Lewis acid have been successfully employed in the allylation, demonstrating increased yields and decreased reaction times. This observation is in agreement with our hypothesis that bifunctional ligands act as a linker between the palladium and Lewis acid, lowering the kinetic barrier in this reaction.

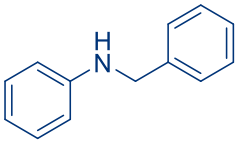
In future work, there is a need to prepare a crystal of bimetallic catalytic species discussed in this chapter. By using X-ray crystallography, it is possible to determine eventual bridging of bifunctional phosphine ligands between two metals, which would be ultimate evidence of hypothesis presented in this chapter. The best approach to achieve that is by using bifunctional crown ether phosphine ligand (3.52), since similar crown ether-lanthanide complexes are already known in the literature.

## 3.4 Experimental section

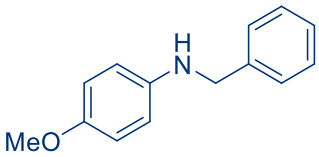
All reactions requiring anhydrous conditions were carried out under nitrogen gas atmosphere using oven-dried glassware. Anhydrous THF was distilled from sodium metal and benzophenone. Tetrakis(triphenylphosphine)palladium(0)[127] and cyclopentadienyl (π-cinnamyl) palladium(II)[118, 128] were prepared according to the reported procedures, All other solvents and reagents were used as received. Column chromatography was carried out on silica gel 230-400 mesh, and analytical TLC on precoated glass plates (silica gel 60, $F_{254}$). $^{1}H$ NMR and $^{13}C$ spectra were recorded on a JEOL ECA 400 MHz in $CDCl_3$ solutions, unless otherwise stated. Chemical shifts are recorded in ppm and coupling constants are recorded in Hz.

### *3.4.1 Monobenzylation of anilines (General procedure **GP1**)*

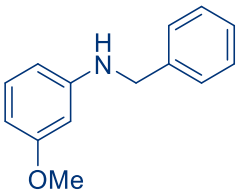
Benzaldehyde (1.5 g, 14.1 mmol, 1 eq.) was added to a stirred solution of aniline (14.1 mmol, 1 eq.) in dichloromethane (25 mL). The reaction mixture was stirred for ten minutes, sodium sulfate (8.03g, 56.5 mmol, 4 eq.) was added, after which the reaction mixture was heated under reflux until completion of the reaction as indicated by TLC. The reaction mixture was cooled to room temperature, filtered, and the solvent was removed under reduced pressure. Obtained product was dissolved in methanol (25 mL), the reaction mixture was cooled to 0°C and sodium borohydride (1.07 g, 2.3 mmol, 2 eq.) was added. The reaction mixture was continued to stir at room temperature and reaction was monitored by TLC. The reaction mixture was quenched with water, concentrated under reduced pressure, extracted with ethyl acetate, washed with water and brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. Obtained residue was purified by column chromatography or by recrystallization.



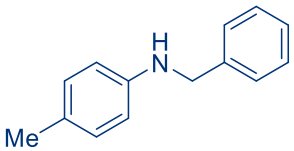
***N-Benzylaniline*[129] *(3.6)* :** Obtained using the general procedure **GP1** in 86% yield as a yellow oil. **$^{1}$H NMR** 400 MHz, $CDCl_3$) δ 7.36 – 7.20 (m, 5H), 7.17 – 7.12 (m, 2H), 6.69 (tt, *J* = 7.7, 1.0 Hz, 1H), 6.63 – 6.57 (m, 2H), 4.27 (s, 2H), 3.81 (br, s, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 148.2, 139.5, 129.3, 128.7, 127.6, 127.3, 117.6, 112.9, 48.3.



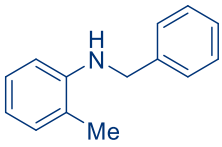
***N-Benzyl-4-methoxyaniline*[129] *(3.7):* :** Obtained using the general procedure **GP1** in 85% yield as a brown solid. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.25 (m, 5H), 6.79 – 6.75 (m, 2H), 6.62 – 6.58 (m, 2H), 4.28 (s, 2H), 3.73 (s, 3H), 3.54 (br, s, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 152.3, 142.5, 139.8, 128.7, 127.6, 127.3, 115.0, 114.2, 56.0, 49.3.



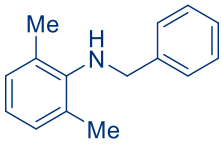
***N-Benzyl-3-methoxyaniline*[130] *(3.8):*** Obtained using the general procedure **GP1** in 55% yield as a yellow oil. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.23 (m, 5H), 7.06 (t, *J* = 8.1 Hz, 1H), 6.29 – 6.22 (m, 2H), 6.18 (t, *J* = 2.3 Hz, 1H), 4.29 (s, 2H), 4.02 (br, s, 1H), 3.73 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 160.9, 149.6, 139.4, 130.0, 128.7, 127.5, 127.3, 106.0, 102.7, 98.9, 55.1, 48.3.



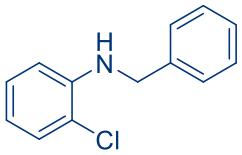
***N-Benzyl-4-methylaniline*[131] *(3.9):*** Obtained using the general procedure **GP1** in 52% yield as a yellow oil. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.20 (m, 5H), 6.95 (d, *J* = 8.5 Hz, 2H), 6.52 (d, *J* = 8.4 Hz, 2H), 4.25 (s, 2H), 3.82 (br, s, 1H), 2.21 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 146.0, 139.7, 129.8, 128.7, 127.6, 127.2, 126.8, 113.1, 77.5, 77.2, 76.8, 48.7, 20.5.



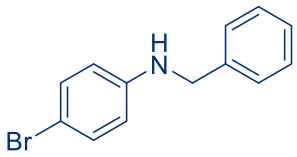
***N-Benzyl-2-methylaniline*[130] *(3.10):*** Obtained using the general procedure **GP1** in 69% yield as a colourless solid. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.25 (m, 5H), 7.13 – 7.05 (m, 2H), 6.68 (t, *J* = 7.4 Hz, 1H), 6.62 (d, *J* = 7.9 Hz, 1H), 4.38 (d, *J* = 5.0 Hz, 2H), 3.85 (s, 1H), 2.17 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 146.2, 139.6, 130.2, 128.8, 127.7, 127.4, 127.3, 122.0, 117.3, 110.1, 77.5, 77.2, 76.8, 48.4, 17.7.



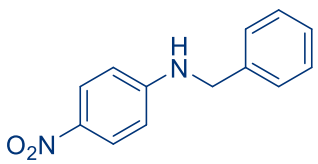
***N-Benzyl-2,6-dimethylaniline*[132] *(3.11):*** Obtained using the general procedure **GP1** in 54% yield as a yellow oil. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.23 (m, 5H), 6.99 (d, *J* = 7.4 Hz, 2H), 6.86 – 6.81 (m, 1H), 4.09 (s, 2H), 3.19 (s, 1H), 2.26 (s, 6H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 146.0, 140.5, 129.9, 128.9, 128.6, 128.0, 127.3, 122.3, 52.9, 18.5.



***N-Benzyl-2-chloroaniline*[130] *(3.12):*** Obtained using the general procedure **GP1** in 52% yield as a yellow oil. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.24 (m, 6H), 7.11 – 7.06 (m, 1H), 6.66 – 6.61 (m, 2H), 4.74 (br, s, 1H), 4.40 (s, 2H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 144.0, 138.9, 129.2, 128.9, 127.9, 127.5, 127.4, 119.2, 117.5, 111.6, 53.6, 48.0.

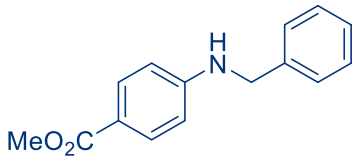


***N-Benzyl-4-bromoaniline*[130] *(3.13):*** Obtained using the general procedure **GP1** in 76% yield as pale brown solid. **$^{1}$H NMR** (400 MHz, $CDCl_3$) 7.36 – 7.18 (m, 7H), 6.49 – 6.44 (m, 2H), 4.26 (s, 2H), 3.91 (br, s, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 147.1, 139.0, 132.0, 128.8, 127.5, 114.5, 109.2, 48.3.

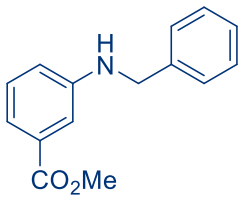


***N-Benzyl-4-nitroaniline*[133] *(3.14):*** Obtained using the general procedure **GP1** in 68% yield as a yellow solid. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 8.11 – 8.06 (m, 2H), 7.40 – 7.29 (m, 5H), 6.60 – 6.55 (m, 2H), 4.88 (br, s, 1H), 4.43 (d, *J* = 5.6 Hz, 2H); **$^{13}$C**

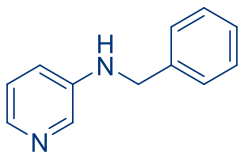
**NMR** (100 MHz, $CDCl_3$) δ 153.2, 138.5, 137.5, 129.1, 128.0, 127.5, 126.5, 111.5, 47.8.



***Methyl 4-(benzylamino)benzoate[133] (3.15):*** Obtained using the general procedure **GP1** in 57% yield as a pale yellow solid. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.8 Hz, 2H), 7.37 – 7.26 (m, 5H), 6.58 (d, *J* = 8.8 Hz, 2H), 4.49 (s, 1H), 4.38 (d, *J* = 5.6 Hz, 2H), 3.84 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 167.4, 151.9, 138.5, 131.7, 128.9, 127.5, 118.7, 111.7, 51.6, 47.8.



***Methyl 3-(benzylamino)benzoate[134] (3.16):*** Obtained using the general procedure **GP1** in 51% yield as a yellow oil. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 6H), 7.21 (t, *J* = 7.9 Hz, 1H), 6.79 (ddd, *J* = 8.1, 2.6, 1.0 Hz, 1H), 4.36 (d, *J* = 4.8 Hz, 2H), 4.15 (s, 1H), 3.88 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 167.6, 148.2, 139.0, 131.2, 129.3, 128.8, 127.7, 127.5, 118.8, 117.3, 113.6, 52.2, 48.3.

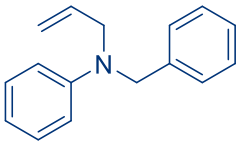


***N-Benzylpyridin-3-amine[130] (3.17):*** Obtained using the general procedure **GP1** in 65% yield as a pale yellow solid. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 2.8 Hz, 1H), 7.97 (dd, *J* = 4.7, 1.2 Hz, 1H), 7.38 – 7.28 (m, 5H), 7.06 (dd, *J* = 8.3, 4.7 Hz, 1H), 6.87 (ddd, *J* = 8.3, 2.8, 1.3 Hz, 1H), 4.35 (d, *J* = 5.7 Hz, 2H), 4.12 (br, s, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 144.1, 139.0, 138.6, 136.3, 128.9, 127.6, 127.5, 123.8, 118.6, 47.9.

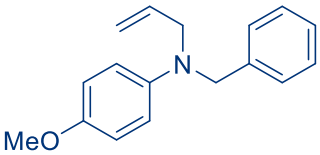
### *3.4.2 Tsuji-Trost Allylation (General procedure **GP2**)*

To a stirred solution of aniline derivative (1 mmol, 1 eq.), $Pd(PPh_3)_4$ (0.05 eq.) and lanthanum triflate (0.1 eq.) in dry THF (5 ml), allyl alcohol (3 eq.) was added. The reaction mixture was heated at reflux for 20 hours under nitrogen. After cooling to the room temperature, the mixture was filtrated through celite, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with hexane/ethyl acetate (75:25).


***N-Allyl-N-methylaniline[135] (3.5):*** Obtained using the general procedure **GP2** in 59% yield as a yellow oil. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.26 – 7.18 (m, 2H), 6.75 – 6.66 (m, 3H), 5.83 (ddt, *J* = 17.2, 10.2, 5.1 Hz, 1H), 5.20 – 5.10 (m, 2H), 3.90 (dt, *J* = 5.0, 1.6 Hz, 2H), 2.92 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 149.6, 133.9, 129.2, 116.5, 116.2, 112.6, 55.4, 38.1.

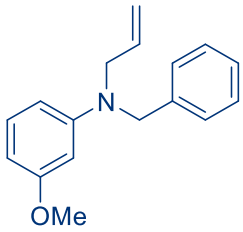



***N-Allyl-N-benzylaniline[136] (3.19):*** Obtained using the general procedure **GP2** in 75% yield as a yellow oil. **$^1$H NMR** (400 MHz, $CDCl_3$) δ7.33 – 7.12 (m, 7H), 6.73 – 6.64 (m, 3H), 5.93 – 5.79 (m, 1H), 5.23 – 5.11 (m, 2H), 4.53 (s, 2H), 3.99 (dt, *J* = 4.7, 1.6 Hz, 2H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 149.1, 139.1, 133.8, 129.3, 128.7, 126.9, 126.7, 116.6, 116.4, 112.5, 54.1, 53.1.

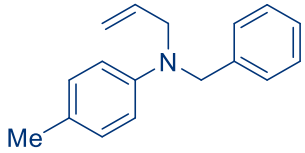



***N-Allyl-N-benzyl-4-methoxyaniline[137] (3.20):*** Obtained using the general procedure **GP2** in 79% yield as a colourless oil. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.20 (m, 5H), 6.81 – 6.75 (m, 2H), 6.71 – 6.66 (m, 2H), 5.87 (ddt, *J* = 17.1, 10.2, 5.1 Hz, 1H), 5.23 – 5.13 (m, 2H), 4.46 (s, 2H), 3.95 – 3.91 (m, 2H), 3.73 (s, 3H); **$^{13}$C NMR**

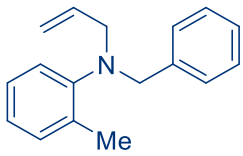
(100 MHz, $CDCl_3$) δ 151.7, 143.8, 139.4, 134.3, 128.6, 127.0, 126.9, 116.5, 114.8, 114.5, 55.9, 55.0, 54.0.



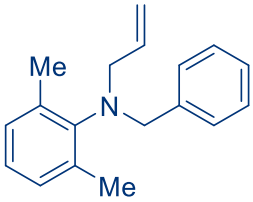

***N-Allyl-N-benzyl-3-methoxyaniline[138] (3.21):*** Obtained using the general procedure **GP2** in 61% yield as a colourless oil. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.20 (m, 5H), 7.08 (t, *J* = 8.0 Hz, 1H), 6.37 – 6.31 (m, 1H), 6.30 – 6.23 (m, 2H), 5.87 (ddt, *J* = 15.3, 5.3, 4.7 Hz, 1H), 5.23 – 5.15 (m, 2H), 4.52 (s, 2H), 3.98 (d, *J* = 4.9 Hz, 2H), 3.72 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 160.8, 150.5, 139.0, 133.7, 129.9, 128.7, 126.9, 126.7, 116.5, 105.7, 101.4, 99.1, 55.1, 54.1, 53.2.



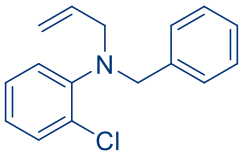

***N-Allyl-N-benzyl-4-methylaniline[139] (3.22):*** Obtained using the general procedure **GP2** in 56% yield as a colourless oil. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.18 (m, 5H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.63 (d, *J* = 8.6 Hz, 2H), 5.93 – 5.79 (m, 1H), 5.21 – 5.13 (m, 2H), 4.50 (s, 2H), 3.96 (d, *J* = 4.9 Hz, 2H), 2.22 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 147.0, 139.3, 134.0, 129.8, 128.7, 126.9, 126.8, 125.8, 116.3, 112.8, 54.3, 53.3, 20.3.



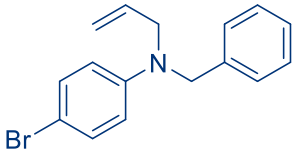

***N-Allyl-N-benzyl-2-methylaniline[139] (3.23):*** Obtained using the general procedure **GP2** in 13% yield as a yellow oil. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.15 (m, 6H), 7.09 (t, *J* = 7.5 Hz, 1H), 7.02 – 6.92 (m, 2H), 5.80 (ddt, *J* = 16.5, 10.3, 6.2 Hz, 1H), 5.16 – 5.05 (m, 2H), 4.12 (s, 2H), 3.51 (dt, *J* = 6.1, 1.2 Hz, 2H), 2.38 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 150.1, 139.1, 135.1, 134.0, 131.2, 128.7, 128.3, 126.9, 126.1, 123.4, 122.3, 117.4, 57.0, 55.6, 18.6.



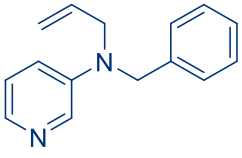

***N-Allyl-N-benzyl-2,6-dimethylaniline (3.24):*** Obtained using the general procedure **GP2** in 6% yield as a colourless oil. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.21 (m, 5H), 7.03 – 6.93 (m, 3H), 5.81 (ddt, *J* = 16.7, 10.0, 6.7 Hz, 1H), 5.14 – 5.00 (m, 2H), 4.15 (s, 2H), 3.59 (d, *J* = 6.7 Hz, 2H), 2.26 (s, 6H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 148.3, 140.1, 137.4, 136.7, 129.1, 129.1, 128.2, 126.9, 125.1, 116.6, 57.0, 55.7, 20.0; **IR (NaCl):** 3063, 3026, 1636, 1593, 1205, 1097; **HRMS (EI)** Exact mass calcd for $C_{18}H_{22}N$ $(M+H)^+$: 252.1752, Found: 225.1747; **MS (ESI):** 252.11 $(M+H)^+$.




***N-Allyl-N-benzyl-2-chloroaniline (3.25):*** NMR yield 16%. Yellow oil. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 6H), 7.10 – 7.05 (m, 1H), 6.64 – 6.60 (m, 2H), 5.99 – 5.88 (m, 1H), 5.32 – 5.15 (m, 2H), 4.39 (s, 2H), 3.82 (tt, *J* = 5.6, 1.6 Hz, 2H); **HRMS (EI)** Exact mass calcd for $C_{16}H_{17}{}^{35}ClN$ $(M+H)^+$: 258.1050, Found: 258.1057; **MS (ESI):** 258.52 $(M+H)^+$.

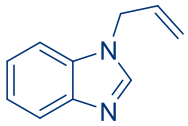



***N-Allyl-N-benzyl-4-bromoaniline[140] (3.26):*** Obtained using the general procedure **GP2** in 11% yield as a colourless oil. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.17 (m, 7H), 6.57 (d, *J* = 9.1 Hz, 2H), 5.85 (ddt, *J* = 16.9, 10.4, 4.8 Hz, 1H), 5.23 – 5.14 (m, 2H), 4.52 (s, 2H), 3.99 (d, *J* = 4.8 Hz, 2H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 148.0, 138.4, 133.2, 131.9, 128.8, 127.1, 126.6, 116.7, 114.2, 108.5, 54.3, 53.4.

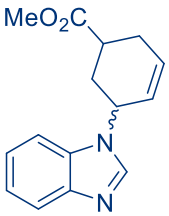



***N-Allyl-N-benzylpyridin-3-amine (3.31):*** Obtained using the general procedure **GP2** in 74% yield as a yellow oil. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 3.0 Hz, 1H), 7.95 (d, *J* = 4.5 Hz, 1H), 7.35 – 7.19 (m, 5H), 7.05 (dd, *J* = 8.5, 4.6 Hz, 1H), 6.97 – 6.91 (m, 1H), 5.92 – 5.79 (m, 1H), 5.24 – 5.14 (m, 2H), 4.55 (s, 2H), 4.05 – 4.00 (m, 2H); **$^{13}$C**

**NMR** (100 MHz, $CDCl_3$) δ 144.8, 138.1, 138.0, 135.2, 132.8, 128.9, 127.3, 126.6, 123.6, 118.8, 117.0, 54.0, 53.1; **IR (NaCl):** 3373, 3061, 3030, 2924, 1582, 1495, 1358, 1242; **HRMS (EI)** Exact mass calcd for $C_{15}H_{17}N_2$ $(M+H)^+$: 225.1392, Found: 225.1389; **MS (ESI):** 225.16 $(M+H)^+$.



***N-Allylbenzimidazole[141] (3.32):*** Obtained using the general procedure **GP2** in 95% yield as a yellow oil. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.84 – 7.79 (m, 1H), 7.39 – 7.34 (m, 1H), 7.31 – 7.25 (m, 2H), 6.07 – 5.94 (m, 1H), 5.32 – 5.14 (m, 2H), 4.80 – 4.74 (m, 2H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 143.9, 142.9, 133.9, 131.9, 123.0, 122.2, 120.4, 118.6, 110.0, 47.4.



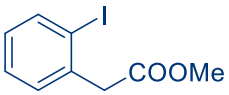
***Methyl 5-(1H-benzo[d]imidazol-1-yl)cyclohex-3-ene-1-carboxylate (3.40):*** Obtained using the general procedure **GP2** as a colourless oil in 91% yield as a 1.7:1 ratio of diastereoisomers. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.93 (s, 2H), 7.85 – 7.78 (m, 2H), 7.49 – 7.40 (m, 2H), 7.34 – 7.24 (m, 4H), 6.32 – 6.25 (m, 1H), 6.15 – 6.08 (m, 1H), 5.93 (m, 1H), 5.88 – 5.79 (m, 1H), 5.18 – 5.08 (m, 2H), 3.64 (s, 6H), 2.95 – 2.85 (m, 1H), 2.66 – 2.05 (m, 13H). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 174.6, 174.1, 144.3, 144.2, 141.9, 141.5, 133.1, 132.5, 132.1, 132.0, 130.5, 128.5, 128.4, 126.2, 123.2, 122.8, 122.7, 122.3, 122.1, 120.5, 110.3, 109.8, 52.5, 52.0, 51.9, 49.0, 38.5, 34.9, 32.2, 30.9, 27.3, 27.2; **IR (NaCl):** 3034, 1728, 1657, 1614, 1211, 1177, 1119; **HRMS (EI)** Exact mass calcd for $C_{15}H_{17}N_2O_2$ $(M+H)^+$: 257.1290, Found: 257.1298; **MS (ESI):** 257.04 $(M+H)^+$.

### *3.4.3 Bifunctional ligand mediated allylation (**GP3**)*

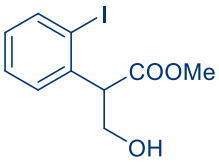
To a stirred solution of cyclopentadienyl (π-cinnamyl) palladium(II) (14.4 mg, 50 μmol, 0.05 eq.), lanthanum triflate (58.5 mg, 0.10 mmol, 0.10 eq.) and the ligand

bifunctional ligand (0.10 mmol, 0.10 eq.) in dry THF (2 mL), the allylic alcohol (204 μL, 174 mg, 3 mmol, 3 eq) and then *N*-methyl aniline (108 μL, 107 mg, 1.00 mmol, 1.00 eq.) were added. The resulting solution was heated to reflux with stirring for a set reaction time. After cooling to room temperature, the mixture was concentrated under vacuum. The resulting dark oil was directly subjected to flash column chromatography on silica gel eluting with hexane/ethyl acetate = 9:1. The products were obtained as a yellow oil.

*3.4.4 Synthetic procedures for the bifunctional crown ether ligand*

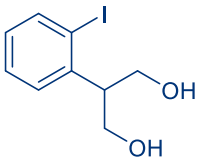



**Methyl 2-(2-iodophenyl)acetate (3.54):** To a stirred solution of 2-iodophenylacetic acid (10 g, 46.6 mmol, 1 eq.) in methanol (65 mL) was added 0.5 mL of concentrated hydrochloric acid. Reaction mixture was heated under reflux for 2.5 h. After that, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting product was extracted with diethyl ether (30 mL) and washed with saturated aqueous $NaHCO_3$ solution (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford ester **3.43** quantitatively as clear oil. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.9 Hz, 1H), 7.34 – 7.24 (m, 2H), 6.98 – 6.92 (m, 1H), 3.80 (s, 2H), 3.71 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 171.0, 139.6, 137.8, 130.7, 129.0, 128.5, 101.1, 52.3, 46.2.

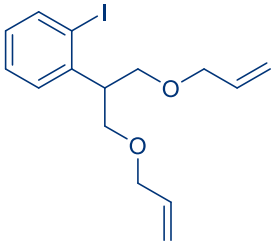



**Methyl 3-hydroxy-2-(2-iodophenyl)propanoate (3.55):** Ester **3.54** (10 g, 43.6 mmol, 1 eq.) and paraformaldehyde (1.44 g, 47.9 mmol, 1.1 eq.) were suspended in DMSO (100 mL) and NaOMe (2.36 g, 43.6 mmol, 1 eq.) was added. The reaction mixture was stirred overnight at room temperature. When the reaction was completed (monitored by TLC), it was poured into ice-cold water (100 mL). The resulting mixture was neutralized with 2N HCl and extracted with ethyl acetate (3×50 mL). The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (solvent system: hexane/ethyl acetate = 1/1) to afford the desired product **3.55** quantitatively as yellow liquid. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.31 (td, *J* = 7.6, 1.2 Hz, 2H), 7.22 (dd, *J* = 7.8, 1.7 Hz, 1H), 4.31 (dd, *J* = 8.5, 4.6 Hz, 1H), 4.02 (dd, *J*

= 11.4, 8.4 Hz, 1H), 3.82 (dd, *J* = 11.4, 4.6 Hz, 1H), 3.73 (s, 3H), 2.66 (s, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 173.6, 140.2, 138.7, 129.5, 128.8, 128.3, 101.5, 63.7, 57.6, 52.5.

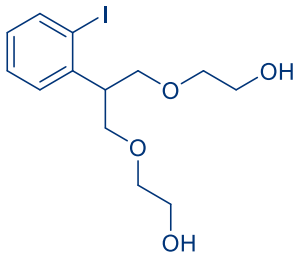


**Methyl 3-hydroxy-2-(2-iodophenyl)propanoate (3.56):** To a stirred solution of **3.55** (8.7 g, 33. 58 mmol, 1eq.) in methanol (100 mL), $NaBH_4$ (3 eq.) was added portion-wise. Reaction mixture was stirred for 4 hours at room temperature, and reaction was monitored by TLC. The reaction mixture was quenched with saturated $NH_4Cl$ solution (20 mL). After quenching, the reaction was concentrated under reduced pressure, extracted with DCM (3×50 mL) and dried over $MgSO_4$. Filtration and removal of solvent afforded product **3.56** (85%) as white solid. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.38 – 7.25 (m, 2H), 6.95 (ddd, *J* = 7.9, 7.1, 1.9 Hz, 1H), 3.83 (dd, *J* = 6.3, 1.9 Hz, 4H), 3.43 (p, *J* = 6.3 Hz, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 144.0, 140.9, 129.5, 129.4, 129.3, 101.3, 63.6, 54.9.

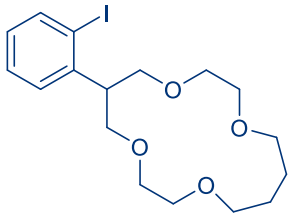


**1-(1,3-bis(Allyloxy)propan-2-yl)-2-iodobenzene (3.57):** To a stirred solution of diol **3.56** (4.42 g, 18.35 mmol, 1 eq.), NaOH (2.94 g, 73.39 mmol, 4 eq.), and $Bu_4N^+Br^-$ (0.59 g, 1.83 mmol, 0.1 eq) in THF (30 mL) was added allyl bromide (6.66 g, 4.76 mL, 55.04 mmol, 3 eq.). The reaction mixture was heated overnight under reflux. When the reaction was completed (according to TLC), reaction mixture was filtered through celite and concentrated under reduced pressure. The residue was purified by flash chromatography (solvent system: hexane/ethyl acetate = 9/1) to afford the desired product **3.57** (77%) as yellow oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.88 – 7.82 (m, 1H), 7.37 – 7.24 (m, 2H), 6.91 (ddd, *J* = 9.0, 4.9, 1.3 Hz, 1H), 5.93 – 5.81 (m, 2H), 5.30 – 5.12 (m, 4H), 4.03 – 3.94 (m, 4H), 3.75 – 3.66 (m, 4H), 3.63 – 3.55 (m, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 142.8, 139.8, 135.0, 128.6, 128.5, 128.3, 116.8, 102.5, 72.1, 70.4, 49.5.

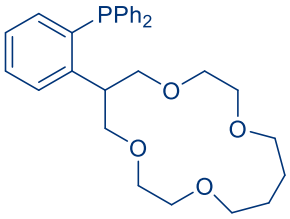



**2,2'-((2-(2-Iodophenyl)propane-1,3-diyl)bis(oxy)) bis(ethan-1-ol) (3.58):** Compound **3.57** (5 g, 16.07 mmol, 1 eq.) was dissolved in methanol (80 mL) and cooled to 0°C. Generated ozone was introduced into the solution, and reaction was monitored by TLC. After the end of the ozonolysis, $NaBH_4$ (1.22 g, 32.13 mmol, 2 eq.) was added, the reaction mixture was warmed to room temperature and monitored by TLC. When completed (according to TLC), water was added (10 mL) in order to quench the excess of $NaBH_4$. After that, the solvent was removed under reduced pressure, the residue was extracted with DCM (3×30 mL) and the combined organic layers were dried over $MgSO_4$. Filtration and removal of solvent afforded product **3.58** (90%) as pale-yellow liquid. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.6 Hz, 1H), 7.40 – 7.21 (m, 2H), 6.94 (ddd, *J* = 8.0, 5.7, 3.3 Hz, 1H), 3.85 – 3.55 (m, 13H), 2.68 (s, 2H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 142.5, 139.9, 128.9, 128.6, 128.1, 102.2, 72.4, 71.8, 61.7, 49.1.




**6-(2-Iodophenyl)-1,4,8,11-tetraoxacyclopentadecane (3.59):** To a stirred solution of diol **3.58** (4.42 g, 18.35 mmol, 1 eq.), NaOH (2.94 g, 73.39 mmol, 4 eq.), and $Bu_4N^+Br^-$ (0.59 g, 1.83 mmol, 0.1 eq) in THF (30 mL) was added 1,4-dibromboutane (6.66 g, 4.76 mL, 55.04 mmol, 3 eq.). The reaction mixture was heated overnight under reflux. When reaction was completed (monitored by TLC), reaction

mixture was filtered through celite and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (solvent system: hexane/ethyl acetate = 75/25) to afford desired product **3.59** (44%) as colourless oil. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.39 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.31 – 7.26 (m, 1H), 6.95 – 6.88 (m, 1H), 3.85 – 3.52 (m, 17H), 1.77 – 1.73 (m, 4H). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 143.1, 139.8, 128.7, 128.6, 128.4, 102.3, 71.4, 71.0, 70.9, 70.5, 49.6, 26.9; **HRMS (EI):** Exact mass calcd for $C_{17}H_{26}O_4I$ $(M+Na)^+$: 443.0696, Found: 443.0698; **MS (ESI):** 479.31 $(M+H)^+$.




**(2-(1,4,8,11-Tetraoxacyclopentadecan-6-yl)phenyl)diphenylphosphane (3.60):** To a solution of the aryl ether (3.0 mmol), Pd(cinn)Cp (17.3 mg, 0.015 mmol, 0.5 mol%), and triethylamine (460 µl, 3.3 mmol) in anhydrous toluene (20 mL) was added diphenylphosphine (522 µL, 3.0 mmol) under nitrogen. The reaction mixture was heated at reflux for 24 hours, cooled to room temperature, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (solvent system: hexane/ethyl acetate = 75/25) to afford the phosphine (51%) as a yellow oil. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.50 (ddd, *J* = 7.8, 4.4, 1.2 Hz, 1H), 7.36 – 7.21 (m, 11H), 7.13 (td, *J* = 7.6, 1.2 Hz, 1H), 6.88 (ddd, *J* = 7.7, 4.0, 1.3 Hz, 1H), 3.94 – 3.37 (m, 17H), 1.76 – 1.66 (m, 4H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 137.0, 136.9, 134.3, 134.1, 133.8, 128.7, 128.6, 128.5, 126.9, 126.8, 71.5, 71.2, 70.8, 70.3, 26.8, 26.8; **$^{31}$P NMR** (100 MHz, $CDCl_3$) δ -15.51; **IR (NaCl):** 3431, 3053, 2858, 1738, 1637, 1435, 1356, 1119; **HRMS (EI):** Exact mass calcd for $C_{29}H_{36}O_4P$ $(M+H)^+$: 279.2351, Found: 479.2343; **MS (ESI):** 479.31 $(M+H)^+$; **IR (KBr):** 3431, 3053, 2858, 1738, 1637, 1435, 1119, 997.

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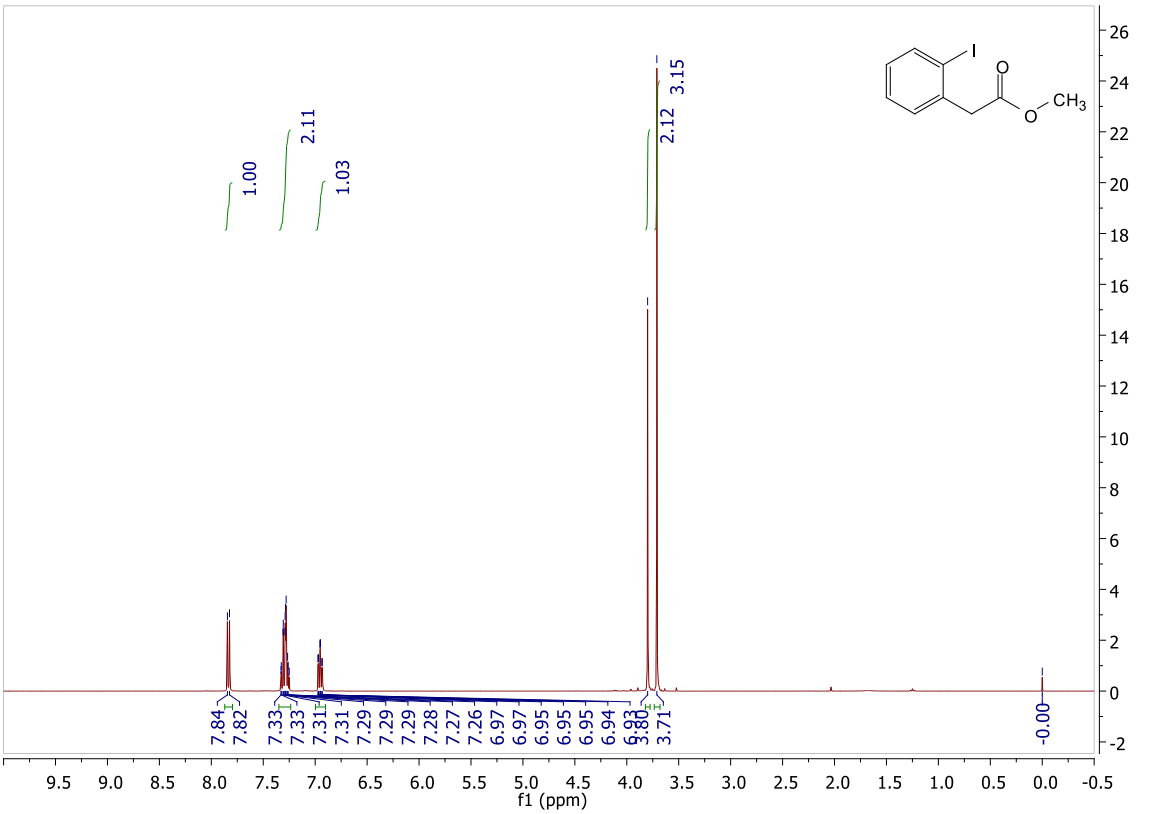
# § Appendix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3.15
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7.84
7.82
7.33
7.33
7.31
7.31
7.29
7.29
7.29
7.28
7.27
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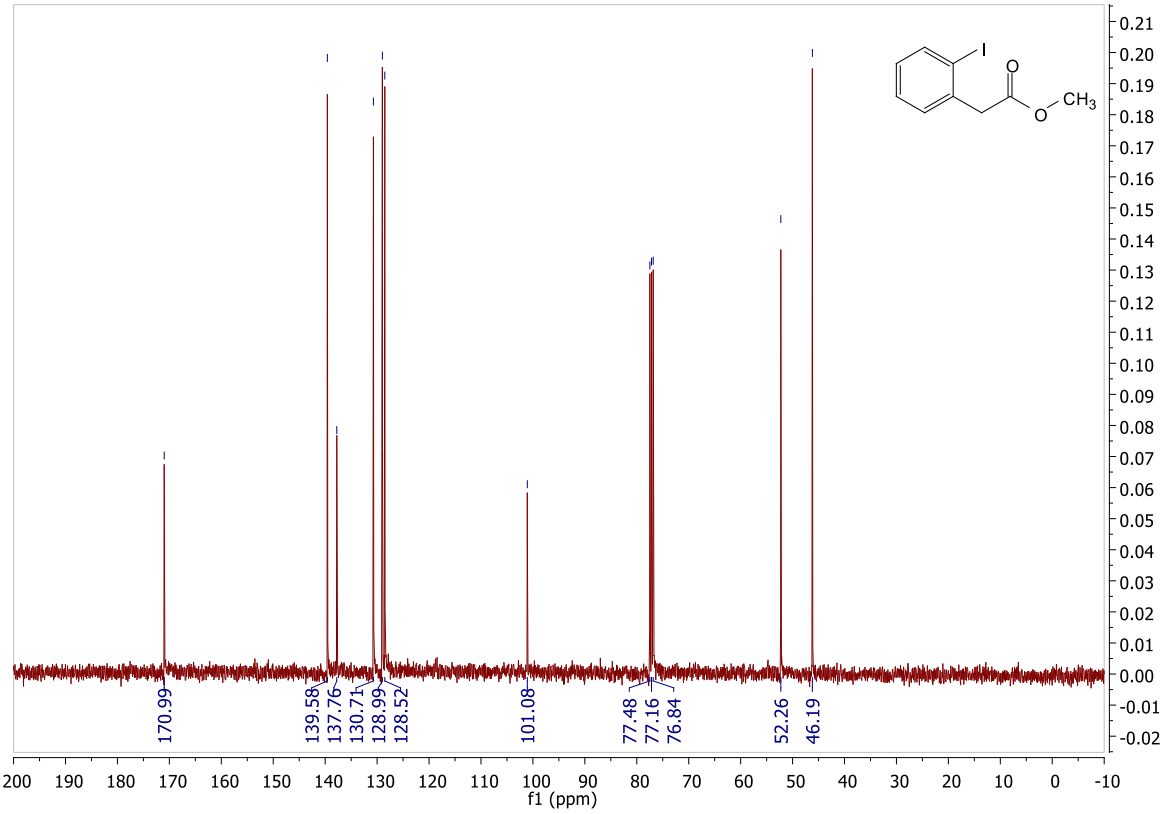
6.97
6.95
6.95
6.95
6.94
3.80
3.71
-0.00
f1 (ppm)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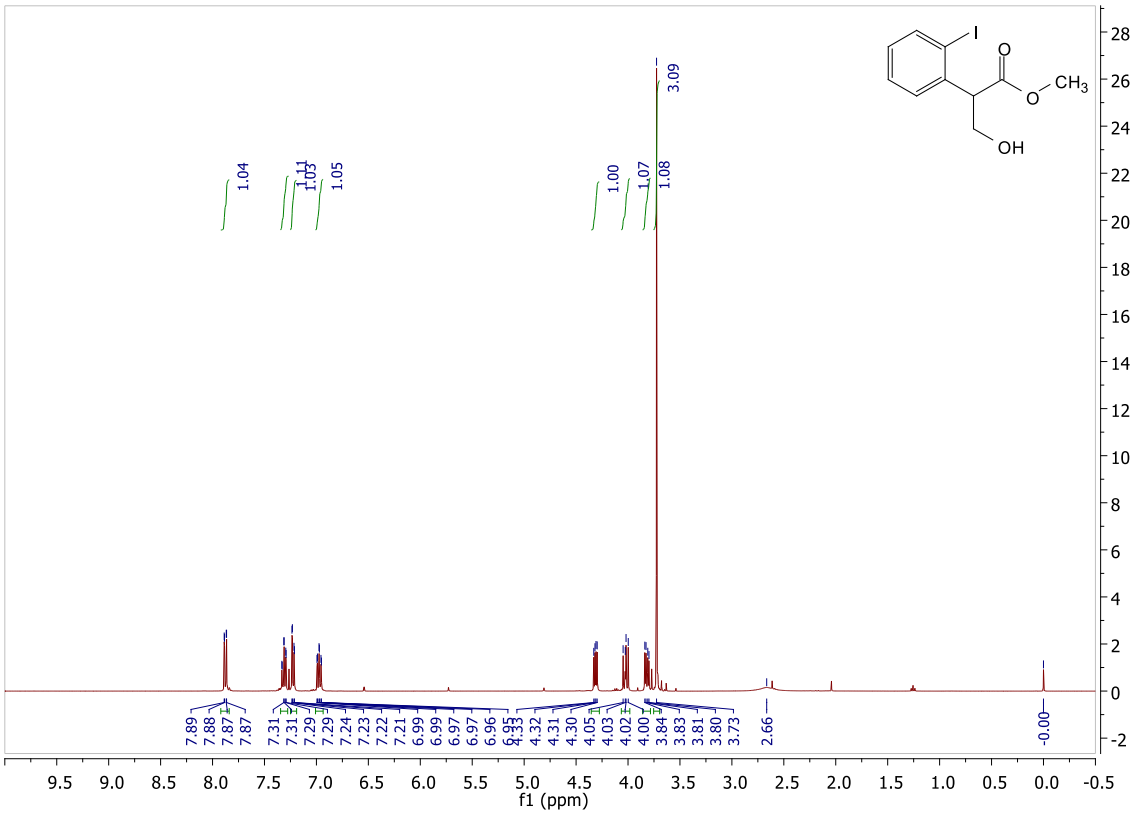
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O
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1.00
1.07
1.08
3.09
7.89
7.88
7.87
7.87
7.31
7.31
7.29
7.29
7.24
7.23
7.22
7.21
6.99
6.99
6.97
6.97
6.96
4.33
4.32
4.31
4.30
4.05
4.03
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4.00
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3.73
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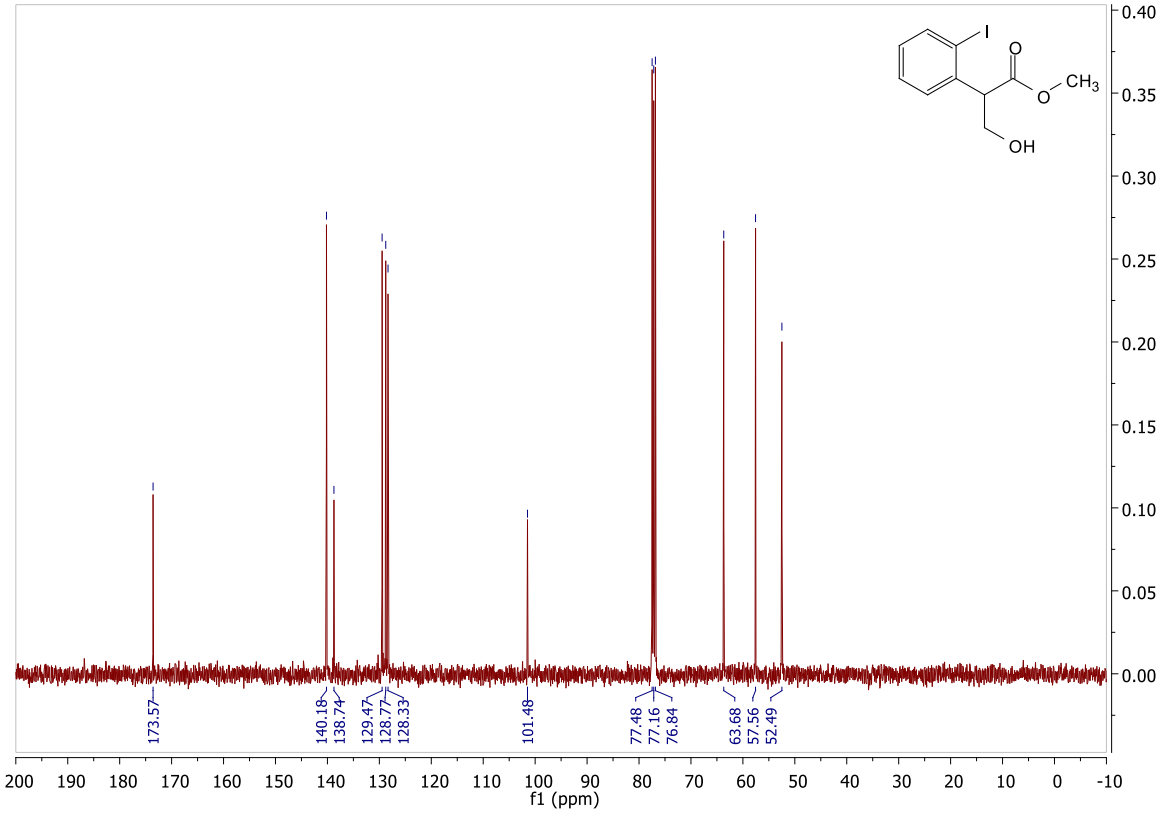
f1 (ppm)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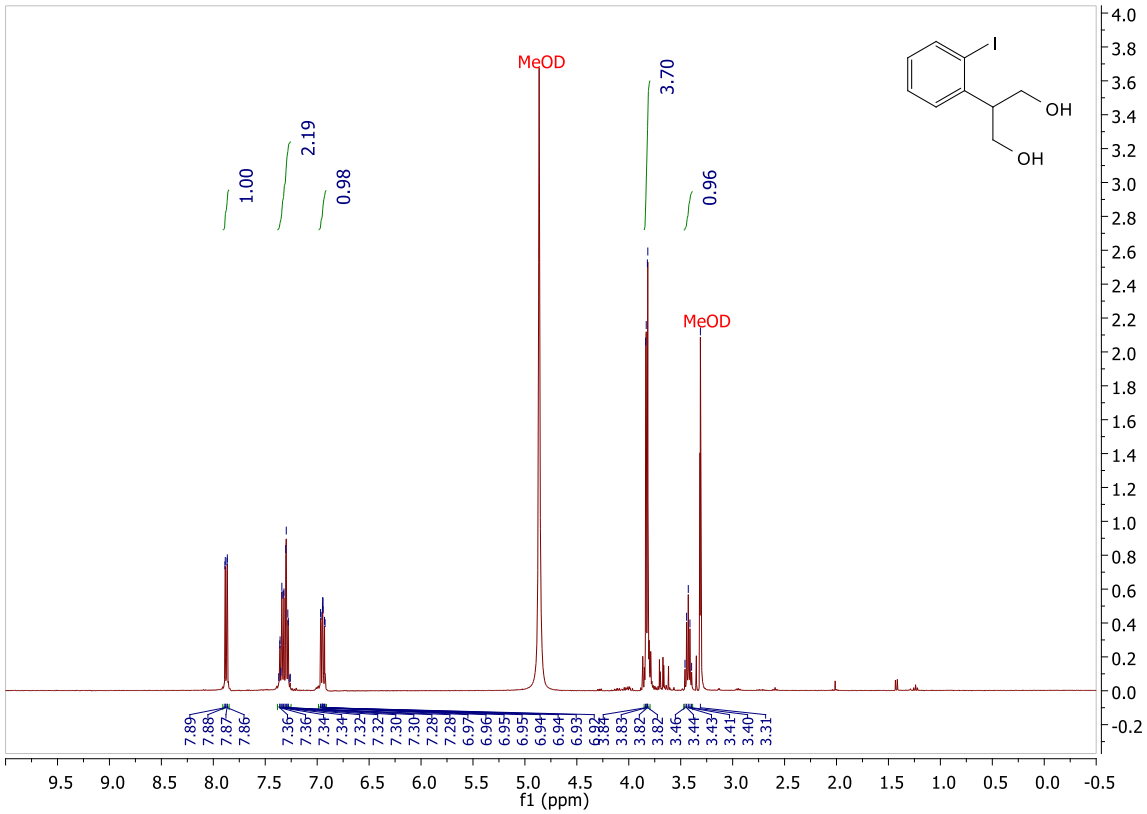
52.49
f1 (ppm)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0.96
MeOD
I
OH
OH
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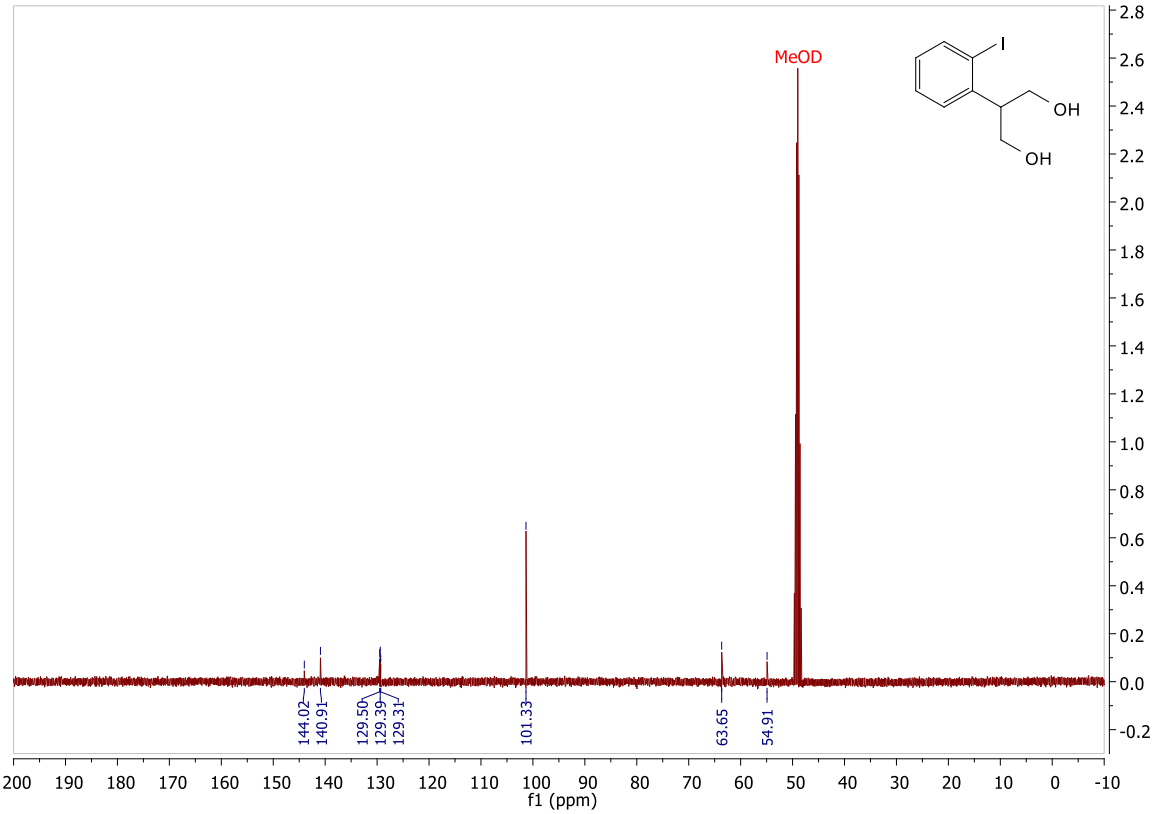
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63.65
54.91
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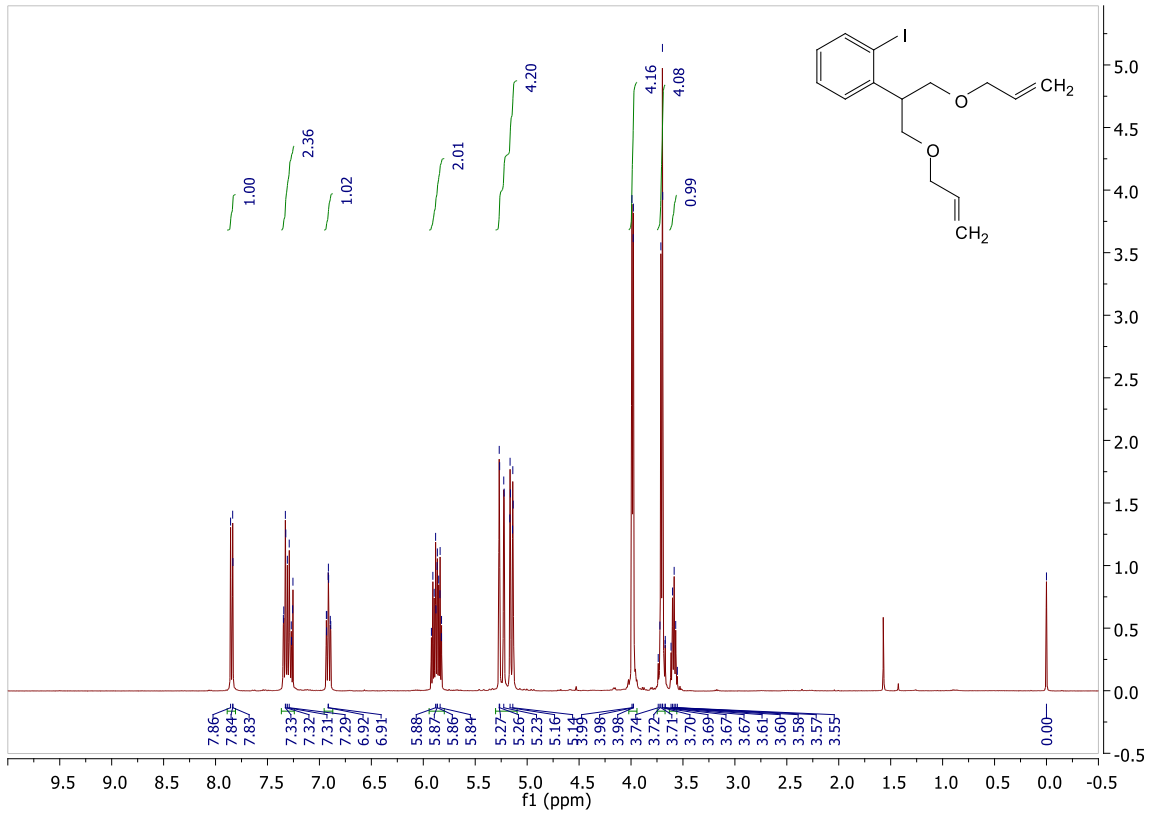
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O
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4.08
0.99
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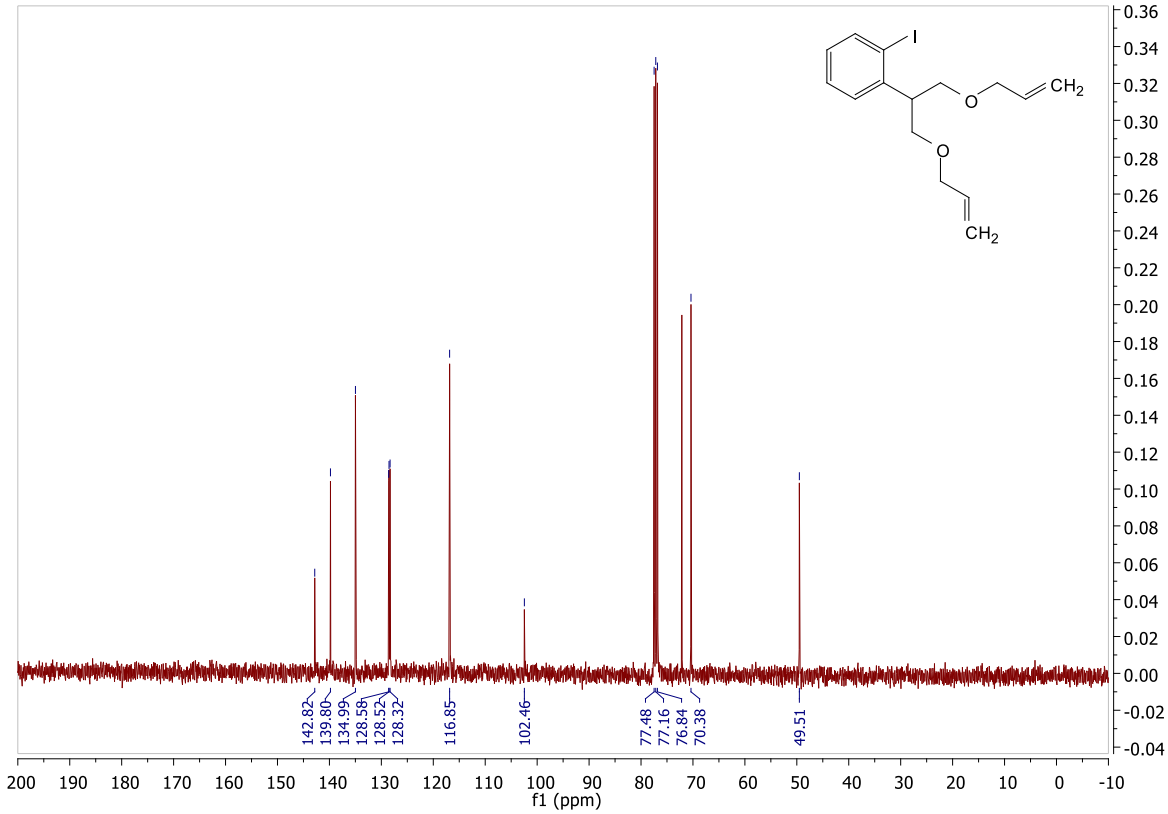
7.84
7.83
7.33
7.32
7.31
7.29
6.92
6.91
5.88
5.87
5.86
5.84
5.27
5.26
5.23
5.16
5.14
3.99
3.98
3.98
3.74
3.72
3.71
3.70
3.69
3.67
3.67
3.61
3.60
3.58
3.57
3.55
0.00
f1 (ppm)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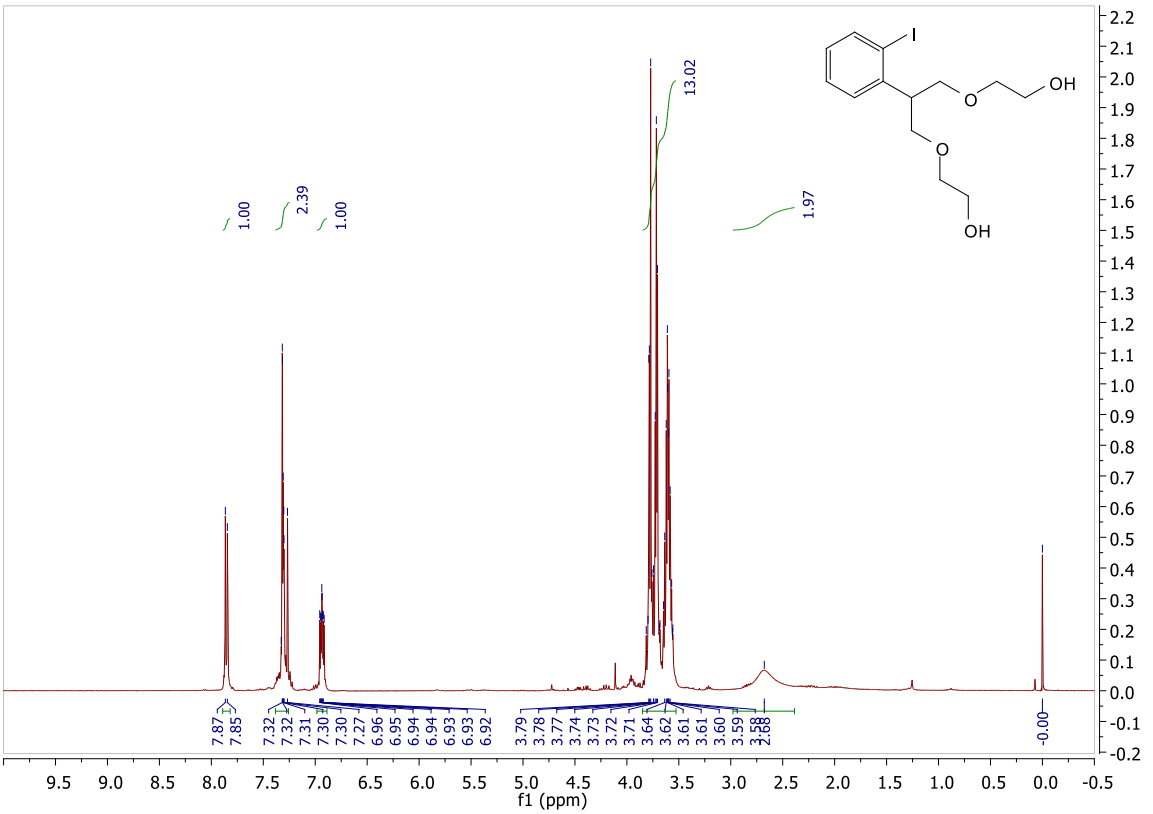
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O
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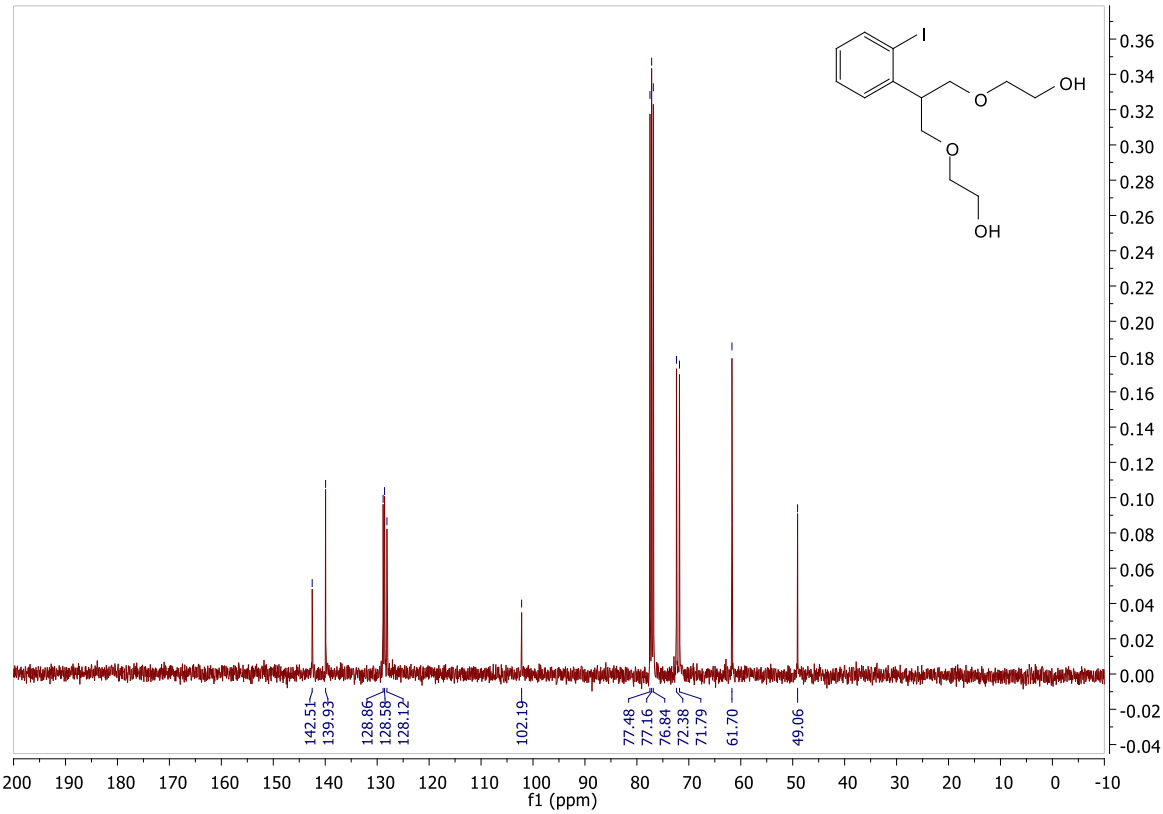
f1 (ppm)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O
OH
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77.16
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72.38
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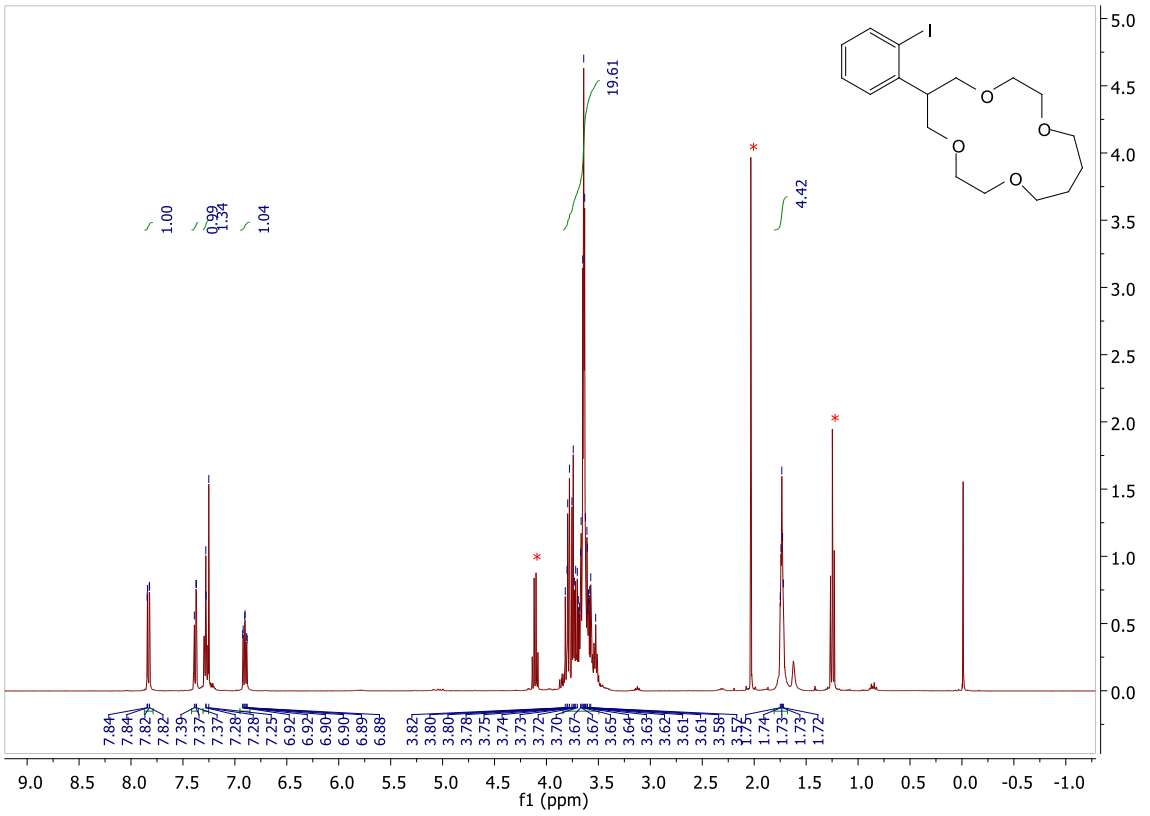
49.06
f1 (ppm)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O
O
O
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1.00
0.99
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1.04
*
*
*
7.84
7.84
7.82
7.82
7.39
7.37
7.37
7.28
7.25
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6.88
3.82
3.80
3.80
3.78
3.75
3.74
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3.72
3.70
3.67
3.67
3.65
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3.61
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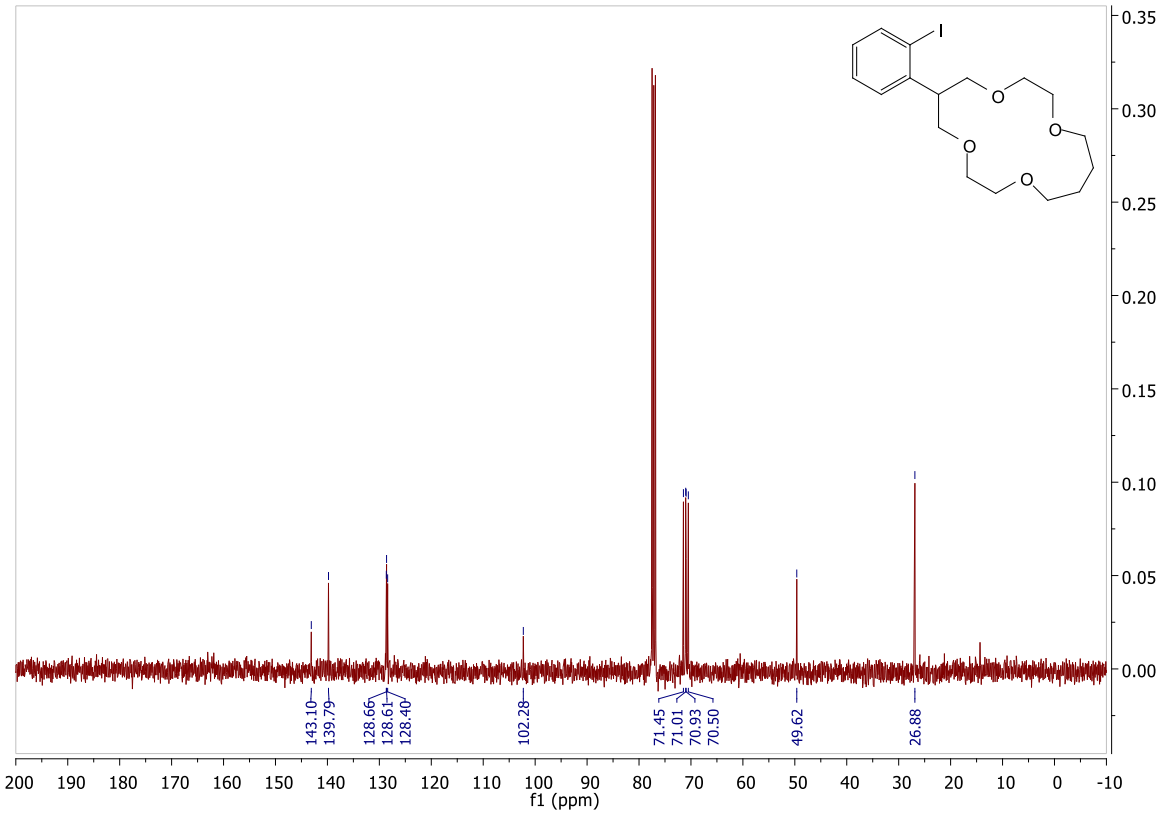
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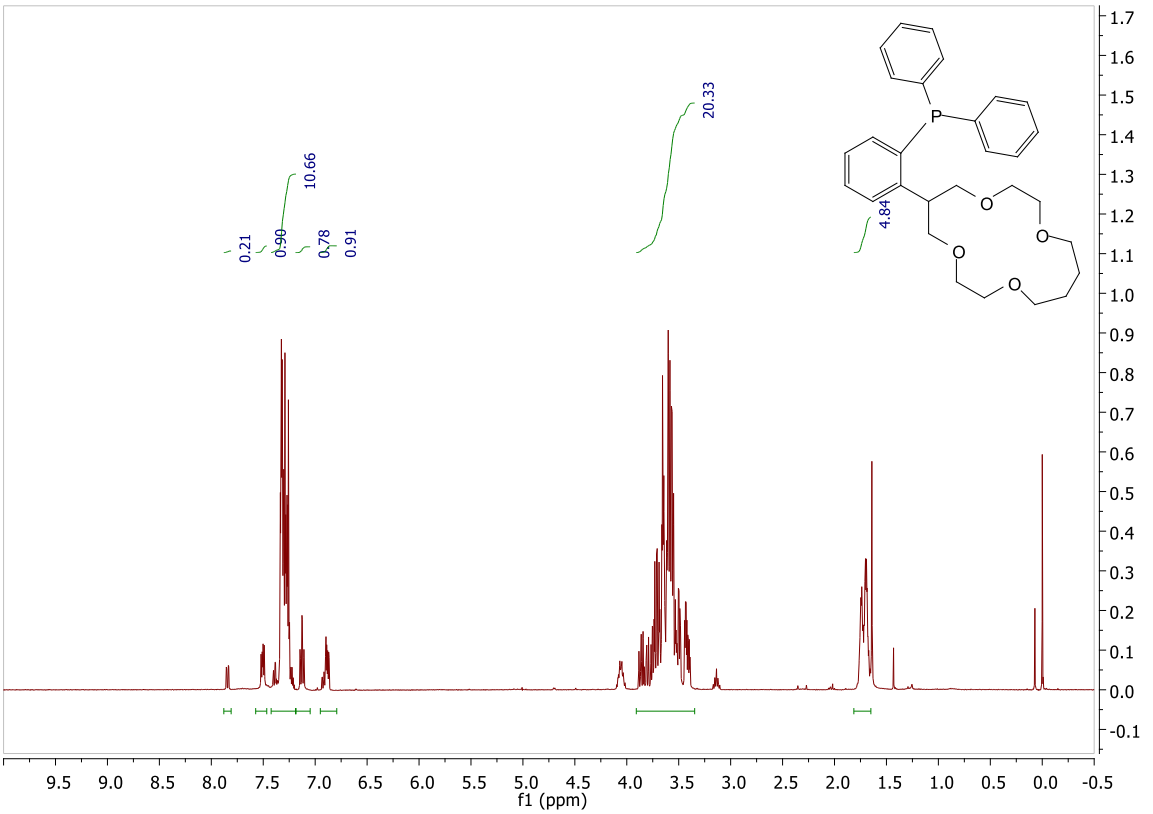
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O
O
O
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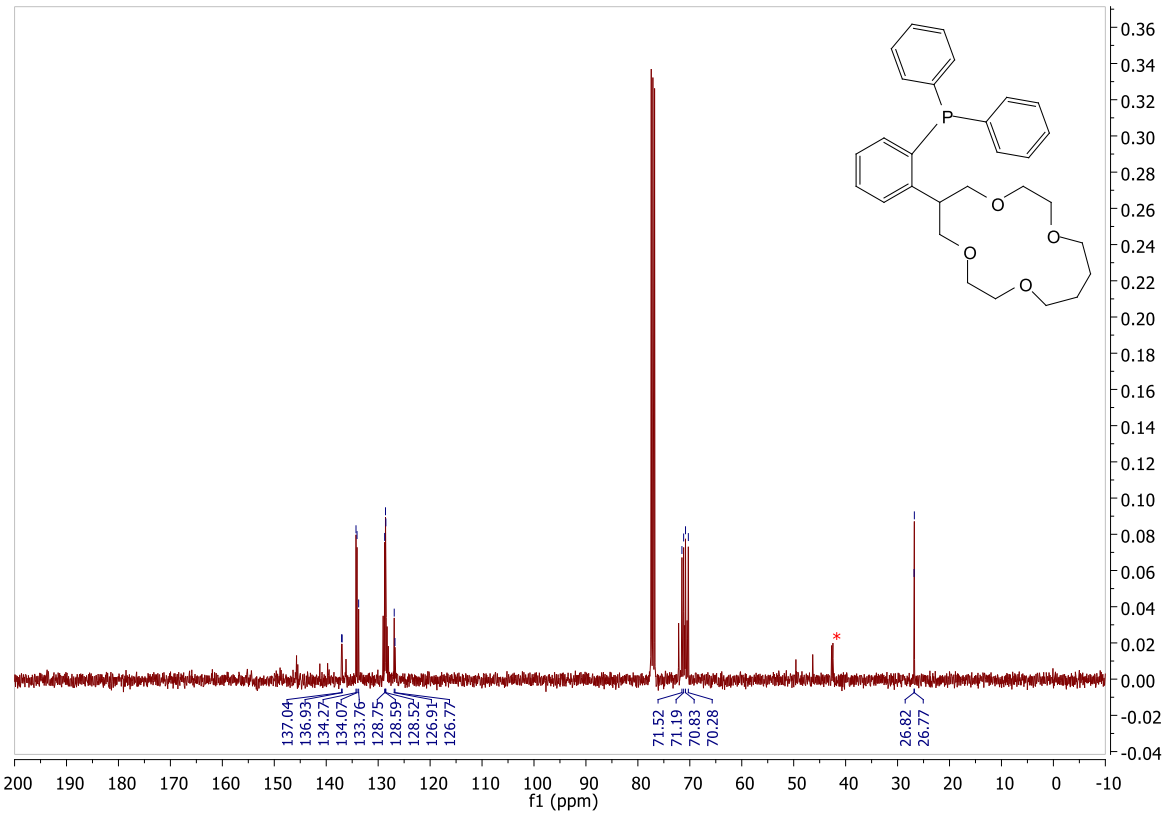
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126.77
71.52
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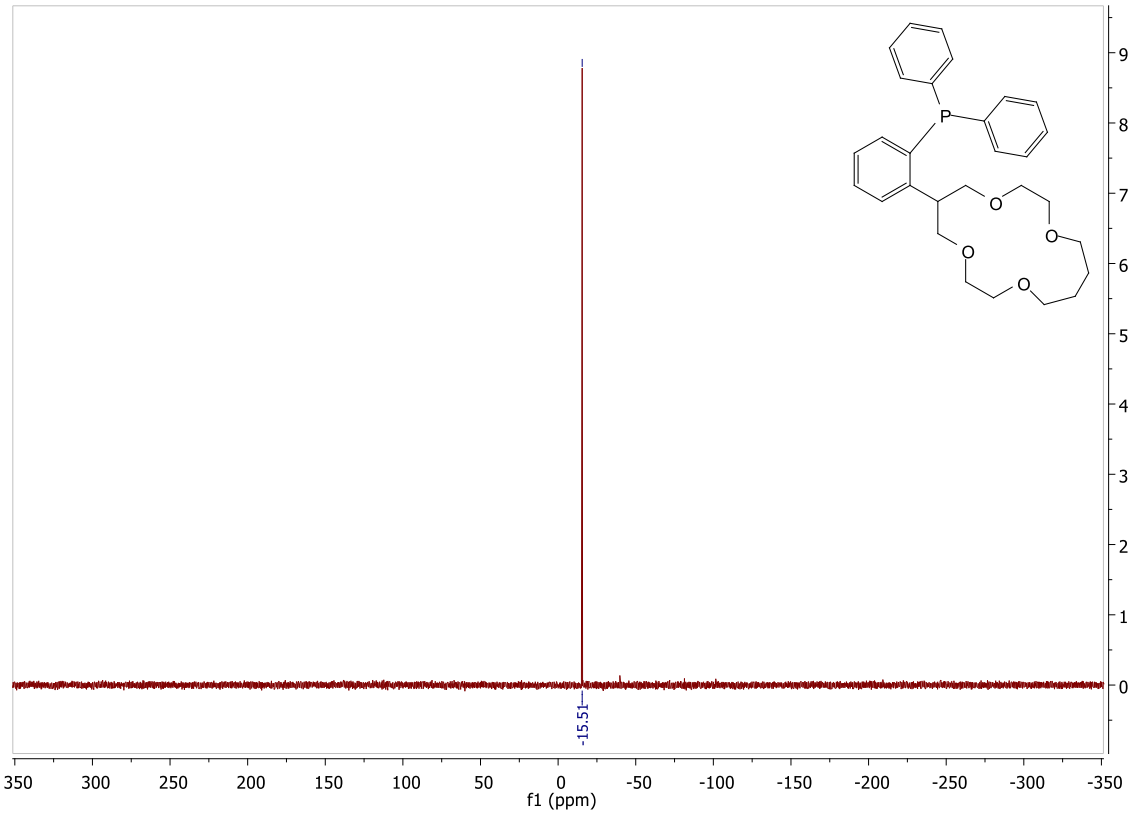
70.83
70.28
26.82
26.77
*
P
O
O
O
O
f1 (ppm)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50
0
-50
-100
-150
-200
-250
-300
-350
f1 (ppm)
9
8
7
6
5
4
3
2
1
0