

**Charles University in Prague**

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**Allylation of  $\alpha,\beta$ -Unsaturated  
Compounds**

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Declaration:

I declare that this thesis is my own independent work and that the results presented in the thesis are original, except as acknowledged in the text. I also declare that the text has not been submitted, either in whole or in part, for a degree at this or any other university.

Prague 30.08.201

Signature

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Kateryna Syedysheva

## List of abbreviations

BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINAPO	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl dioxide
BINOL	1,1'-Bi-2-naphthol
BOROXIN	2,4,6-trihydroxy-1,3,5,2,4,6-trioxatriborinane
$\delta$	chemical shift
DCM	dichloromethane
DIBAL-H	diisobutylaluminium hydride
DIFLUORPHOS	(2,2,2',2'-tetrafluoro-4,4'-bibenzo[ <i>d</i> ]-[1,3]dioxole-5,5'-diyl)bis-(diphenylphosphane)
DIPEA	diisopropylethylamine
DME	dimethoxyethane
DMF	<i>N,N</i> -dimethylformamid
MS	mass spectrum or molecular sieves
ee	enantiomeric excess
eq	equivalent
Et	ethyl
GC	gas chromatography
h	hour
HR-MS	high resolution mass spectrometry
<i>i</i> -	<i>iso</i> -
IR	infrared spectroscopy
m	multiplet
Me	methyl
NMR	nuclear magnetic resonance

Ph	phenyl
Pr	propyl
r.t.	room temperature (20-25 °C)
<i>t</i> -	<i>tert</i> -
TBAI	tetrabutylammonium iodide
Tf	trifluoromethanesulfonate
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TRIP-PA	3,3'-di-(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2' diylhydrogen phosphate

## 1. Introduction

This work is devoted to synthesis of a compound possessing the 6-6-6 condensed ring scaffold with the angular formyl group. This tricyclic framework could potentially be used as an intermediate for the synthesis of icetaxanes. The syntheses of natural compounds are, in general, a very important element in organic chemistry. Particularly, the synthesis of icetaxanes is at the center of increased synthetic efforts nowadays. The icetaxanes are a family of diterpenoid natural products, which have been isolated from a variety of terrestrial plant sources. Their characteristic structural feature is the 6-7-6 condensed ring framework. Icetaxanes are interesting targets, because of their unique, quite complex structure and biological activity. For example, it has been recently found that they exhibit potent cytotoxic activity against colon cancer cell lines (HT-29).<sup>1</sup>

It was envisioned that the synthesis of the 6-6-6 condensed ring framework with aromatic A-ring, could be accomplished from a bicyclic  $\alpha,\beta$ -unsaturated aldehyde by the two key reactions. Firstly, by the allylation of the corresponding  $\alpha,\beta$ -unsaturated carbonyl compounds followed by the oxy-Cope rearrangement and ensuing  $\alpha$ -allylation followed by ring closing metathesis.

In this work I will discuss mainly enantioselective allylations of  $\alpha,\beta$ -unsaturated carbonyl compounds and the oxy-Cope rearrangement. Furthermore, a novel synthesis of 6-6-6 condensed ring framework will be outlined as well.

## 2. The current state of the art

The catalytic enantioselective synthesis has been rapidly advancing, due to the high demand of enantiopure compounds. Over the past 10 years, the field of asymmetric synthesis has taken a major step forward. In 2001 Nobel Prize for Chemistry was awarded to William S. Knowles and Ryoji Noyori for their work on catalytic asymmetric hydrogenation reactions and to K. Barry Sharpless for the development of catalyzed asymmetric oxidation. Both processes are key reactions, allowing the synthesis of a plethora of molecules of industrial and medical importance in pure enantiomeric forms.<sup>2</sup>

The majority of asymmetric transformations employ chiral transition metal catalysts that allow the formation of pure enantiomers from achiral substrates. The usual mode of action relies on the activation of a substrate by transition metal complexes through coordination to the metal center.<sup>2</sup>

In this introduction, typical examples of catalytic and stoichiometric enantioselective allylations of carbonyl compounds by various organometallic reagents are outlined. The reaction is very valuable in organic synthesis, because, besides the formation of a new carbon-carbon bond, it also results in new alcohol functionality.<sup>3</sup>

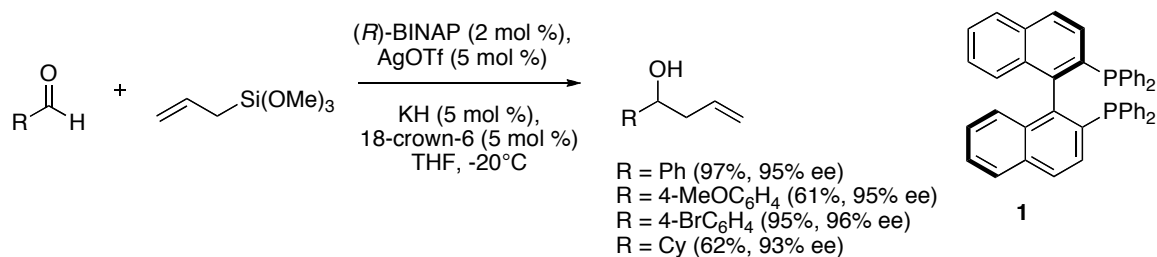
### 2.1. Enantioselective Allylation with Allylic Silanes

#### 2.1.1 Lewis acid catalyzed allylation reactions.

**Ag(I) catalyzed allylation.** H. Yamamoto and coworkers have introduced the allylation of aldehyde with allyltrimethoxysilane, as the allylating reagent, and catalytic amount of KF, 18-crown-6, BINAP **1** and silver (I) triflate (Scheme 1). The

reaction was carried out in THF at  $-20^{\circ}\text{C}$ . A number of BINAP derivatives were evaluated, to see which one gave the highest enantioselectivity and chemical yield. Overall (*R*)-BINAP **1** showed to be the most effective. The reaction with BINAP was performed on a number of substrates. The highest enantioselectivity was obtained on benzaldehyde, with 95% ee and 97% chemical yield.<sup>4</sup>

**Scheme 1.** Ag(I) catalyzed allylation of aldehydes.

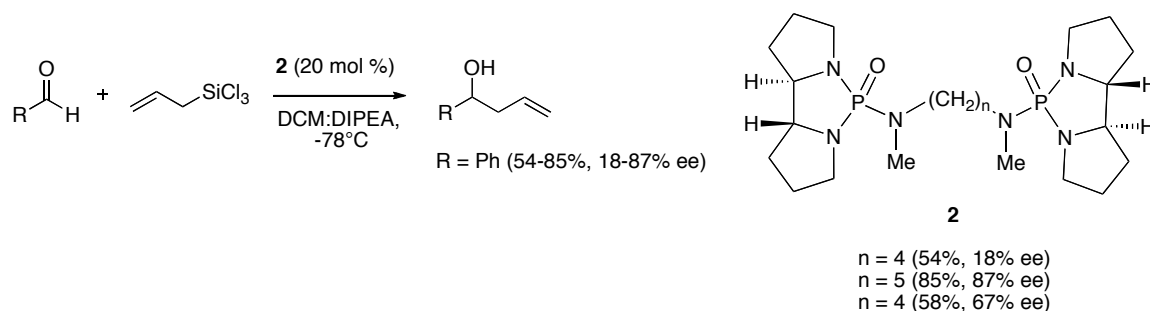


### 2.1.2 Lewis base catalyzed allylation reactions.

**Phosphoramides catalyzed allylation.** Denmark *et. al.* prepared a number of chiral bisphosphoramides to evaluate their activity for the enantioselective allylation of aldehydes. The allylation was performed on benzaldehyde with allyltrimethylsilane in a 1:1 mixture of dichloromethane and DIPEA at  $-78^{\circ}\text{C}$  (Scheme 2). The chiral bisphosphoramide with 2,2'-bispyrrolidine skeleton **2** showed to be the most effective. The reaction on benzaldehyde resulted in 85% chemical yield and 87% ee.<sup>5</sup>

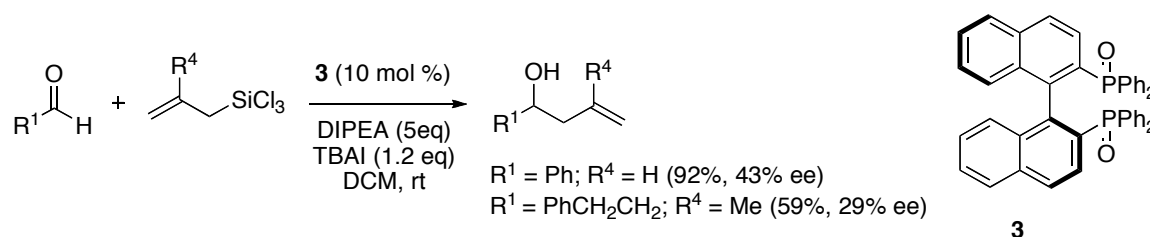


**Scheme 2.** Bisphosphoramides catalyzed allylation.



**Phosphane oxides catalyzed allylation.** Nakajima *et. al.* have introduced the allylation of aldehydes with phosphane oxide (*S*)-BINAPO **3** and allyltrichlorosilane, as allyl agent. The reaction was carried out in presence of DIPEA and tetrabutylammonium iodide (TBAI) in dichloromethane at room temperature (Scheme 3). The reaction was evaluated on a number of substrates. The highest enantioselectivity was obtained on benzaldehyde, with 43% ee and 92% chemical yield.<sup>6,7</sup>

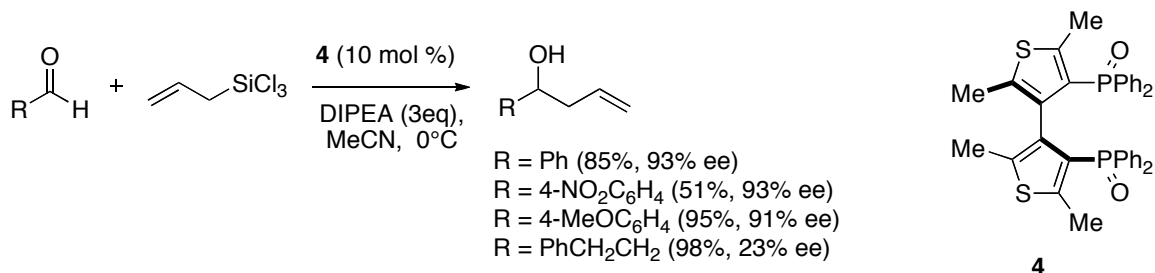
**Scheme 3.** (*S*)-BINAPO catalyzed allylation of aldehydes.



Simonini *et. al.* showed that the heteroaromatic diphosphane oxide (*S*)-**4** could be used for a successful enantioselective allylation of aromatic aldehydes bearing both electron-withdrawing and electron-donating groups. The reaction was carried out in presence of DIPEA in acetonitrile at 0°C, and resulted in the formation of the alcohols with ee<sub>s</sub> higher than 90% and good chemical yields (Scheme 4). The reaction was

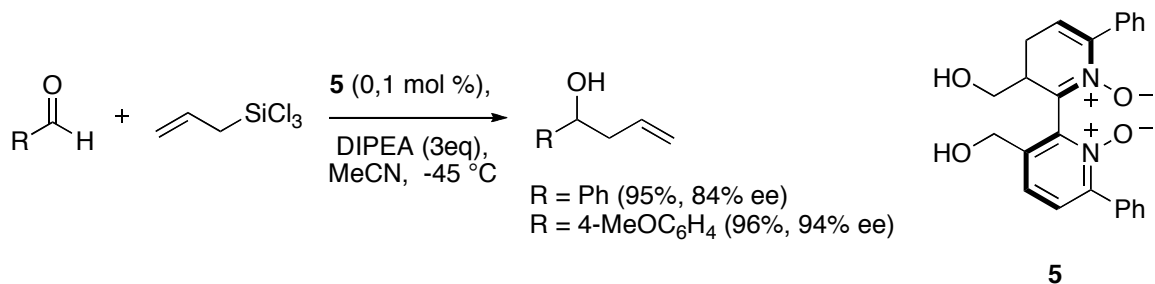
performed on a number of substrates. The highest enantioselectivity was obtained on benzaldehyde, with 93% ee and 85% chemical yield.<sup>8</sup>

**Scheme 4.** Heteroaromatic diphosphane oxide (*S*)-**4** catalyzed allylation of aldehydes.



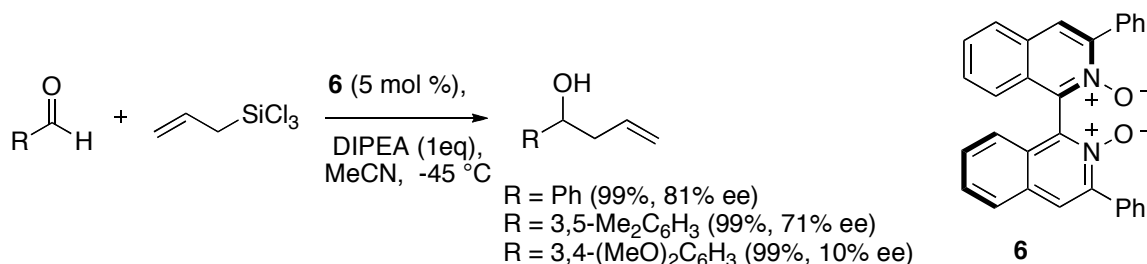
***N,N*-Oxides catalyzed allylation.** Hayashi and coworkers introduced the use of *N,N*-dioxides in the allylation of aldehydes. Compound **5** in presence of DIPEA was used with allyltrichlorosilane in acetonitrile at -45°C (Scheme 5). The result of allylation was very successful. The best result was obtained for the allylation of benzaldehyde, with enantiomeric excess as high as 91% and 95% chemical yield. However, the *N,N*-dioxide **5** worked predominantly on aromatic aldehydes bearing electron-donating groups, resulting in low enantioselectivity and yields on aliphatic aldehydes, and aldehydes with electron-withdrawing groups.<sup>9,10</sup>

**Scheme 5.** *N,N*-dioxide **5** catalyzed allylation of aldehydes.



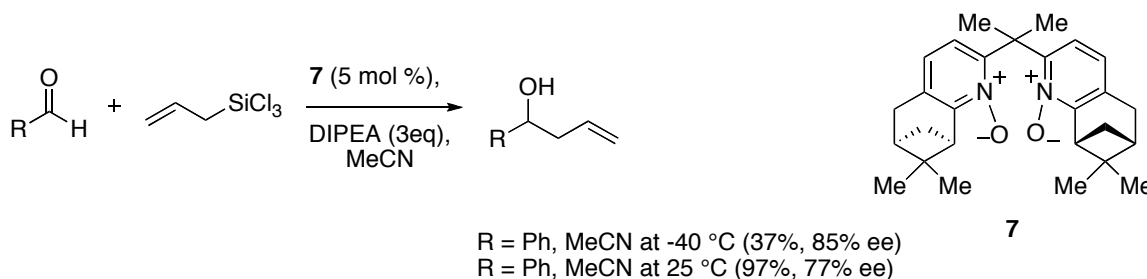
Kocovsky introduced *N,N'*-dioxide **6**, which, on the contrary, under the same reaction conditions showed higher yields and enantioselectivity with electron-poor aromatic aldehydes (Scheme 6).<sup>11</sup>

**Scheme 6.** *N,N'*-dioxide **6** catalyzed allylation of aldehydes.



Chelucci *et al.* reported the use of *N,N'*-dioxides, which possess an isopropylidene backbone between two pyridine rings (the bis-(*N*-oxidoquinoline) derivative **7**). The *N,N'*-dioxide **7**, in the presence of DIPEA, was used for the allylation of benzaldehyde with allyltrichlorosilane in acetonitrile at -40°C (Scheme 7). The reaction resulted in moderate enantiomeric excess (85%) and low chemical yields (37%).<sup>12</sup>

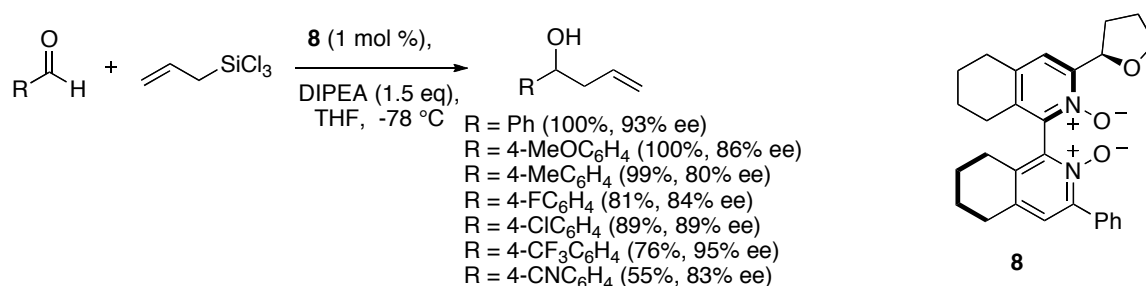
**Scheme 7.** Bis-(*N*-oxidoquinoline) **7** catalyzed allylation of aldehydes.



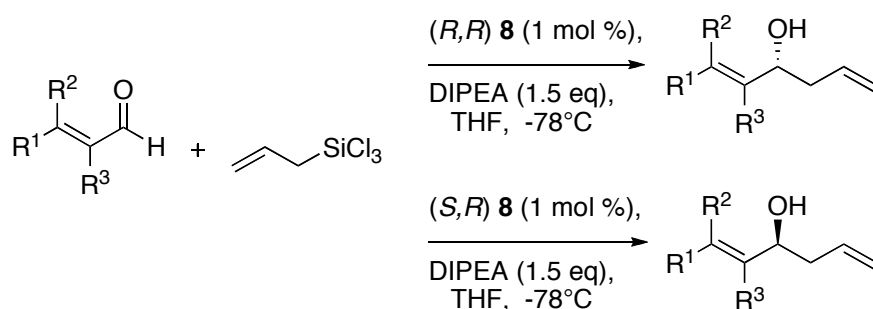
Kotora and coworkers developed a new class of axially chiral bipyridine *N,N'*-dioxides with a bis(tetrahydroisoquinoline) framework (*R,R*)-**8**. In the suggested

protocol, the aldehydes were treated with (*R,R*)-**8** in the presence of DIPEA and allyltrichlorosilane, as allylating agent. Several substrates, both aliphatic and aromatic aldehydes, were tested, as well as the effect of a solvent on enantioselectivity and chemical yield was evaluated. In case of benzaldehyde, the highest enantiomeric excess (above 90%) was obtained in THF at -78°C (Scheme 8).<sup>13</sup>

**Scheme 8.** Chiral *N,N'*-dioxide (*RR*)-**8** catalyzed allylation of aldehydes.



In later work, Kotora *et.al.* evaluated the catalytic activity of *N,N'*-dioxides (*R,R*)-**8** and (*S,R*)-**8** on  $\alpha,\beta$ -unsaturated aldehydes with allyltrichlorosilane. The reactions were carried out under the optimized conditions, in THF at -78 °C. The highest enantioselectivity and chemical yield for (*R,R*)-**8** catalyst was observed on (*E*)-hept-2-enal, with 90 % yield and 99 % ee. The best result for (*S,R*)-**8** catalyst was obtained with the substrate (*E*)-2-methyl-3-phenylacrylaldehyde, with 99 % chemical yield and 97.2 % enantiomeric excess (Table 1).<sup>14</sup>

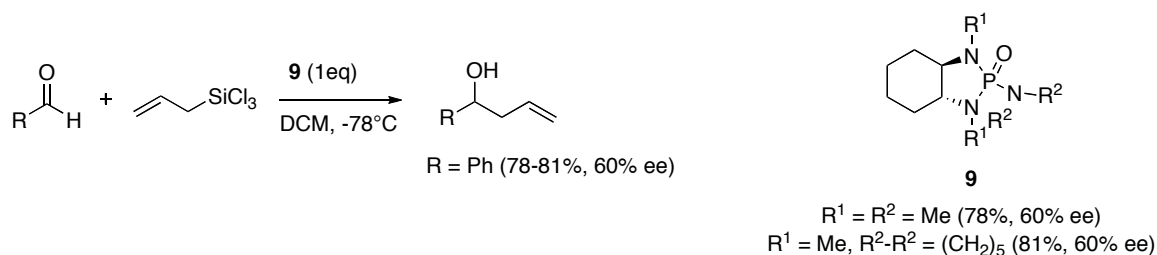
**Table 1.** Chiral *N,N'*-dioxide **8** catalyzed allylation of  $\alpha,\beta$ -unsaturated aldehydes.

$R^1$	$R^2$	$R^3$	<i>(R,R)</i> <b>8</b>		<i>(S,S)</i> <b>8</b>	
			Yield (%)	ee (%)	Yield (%)	ee (%)
Ph	H	H	92	97.4	95	93
Ph	H	Me	90	88.6	99	97.2
Ph	H	Cl	35	92	35	93.6
4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	H	H	60	86.6	60	39.2
4-MeOC <sub>6</sub> H <sub>4</sub>	H	H	80	81.6	80	63
Et	H	H	85	99	90	96
<i>n</i> -Bu	H	H	90	99	95	96.2
H	H	Me	20	28.6	25	94.6
Et	H	Me	70	19.2	90	96.2

### 2.1.3. Stoichiometric enantioselective addition of allylic silanes.

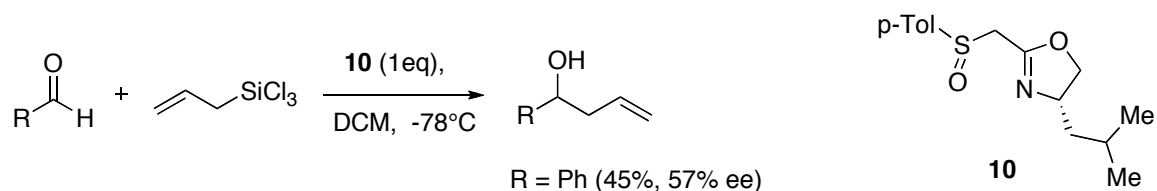
**Phosphoramides mediated allylation.** Denmark and coworkers were the first to introduce the use of chiral phosphoramides as bases for enantioselective allylation of aldehydes. A number of chiral phosphoric triamides with allyltrimethylsilanes in DMF were studied, however, the enantioselectivity was moderate (~60% ee) (Scheme 11).<sup>15</sup>

**Scheme 11.** Phosphoric triamide mediated allylation of aldehydes.



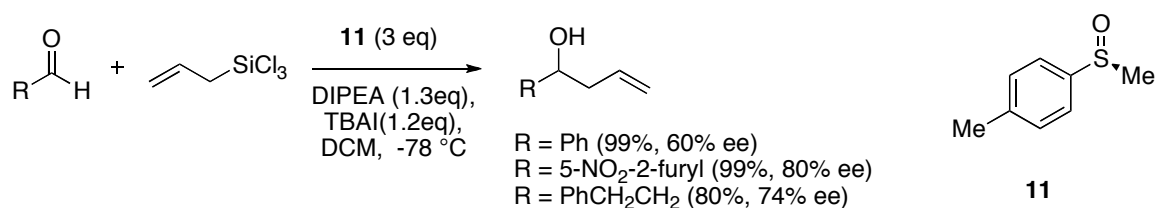
**Sulfoxides mediated allylation.** The first use of sulfoxides as Lewis base promoters for the allylation of aldehydes was introduced by Rowlands and Barnes. The allylation was performed on benzaldehyde with allyltrichlorosilane in dichloromethane at -78 °C (Scheme 12). The chiral oxazolinylsulfoxide **10** showed to be moderately effective in terms of enantioselectivity and chemical yield (57% ee<sub>s</sub> and 45% yield).<sup>16</sup>

**Scheme 12.** Oxazolinylsulfoxide (*S*)-**10** mediated allylation of aldehydes.



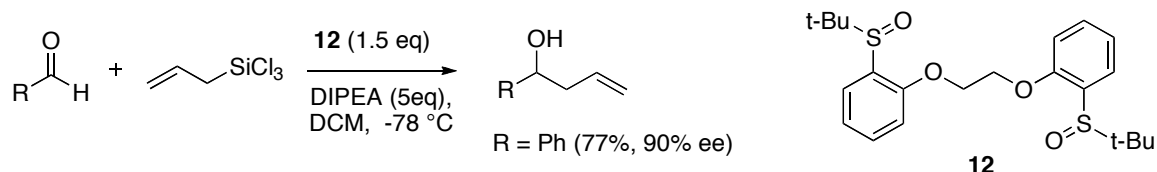
Shortly afterward, Massa and Scettri reported a (*R*)-methyl *para*-tolylsulfoxide ((*R*)-**11**) promoter. Based on Nakajima's work, it was successfully used in the presence of tetrabutylammonium iodide (TBAI) and DIPEA. The reaction was carried out with allyltrichlorosilane in dichloromethane at -78°C, providing the homoallylic alcohols in chemical yields higher than 95% and over 80% enantiomeric excess (Scheme 13).<sup>17</sup>

**Scheme 13.** Sulfoxide **11** mediated allylation of aldehydes.



Liao and coworkers reported the enantioselective allylation of aldehydes by a number of enantiomerically pure mono and bisaryl *tert*-butyl sulfoxides. The bissulfoxide **12** with a two-carbon ether was the most effective in terms of enantioselectivity and chemical yield. The reaction, performed on benzaldehyde with allyltrichlorosilane in dichloromethane at -78°C, resulted in the formation of chiral alcohol with 90 % ee<sub>s</sub> and in 77 % yield (Scheme 14).<sup>18</sup>

**Scheme 14.** Bis-sulfoxide **12** mediated allylation of aldehydes.

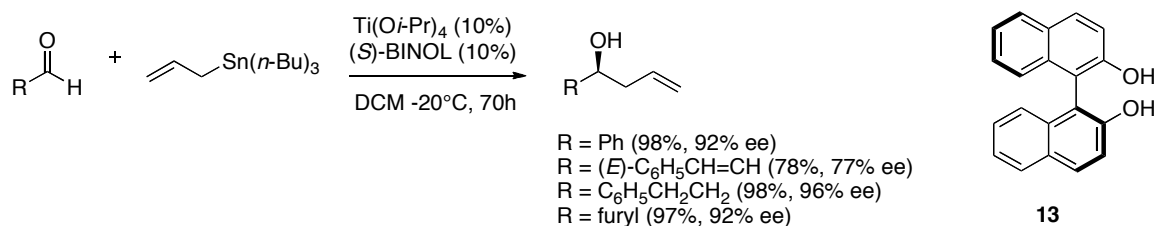


## 2.2. Catalytic enantioselective addition with allylic stannanes

### 2.2.1. Lewis acid catalyzed allylation reactions.

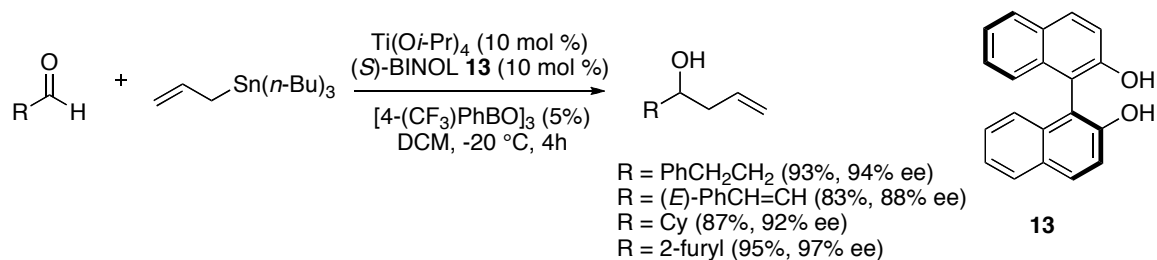
**Ti(IV) catalyzed reactions.** Keck *et. al.* developed an interesting method of Lewis acid-promoted additions of allylstannanes. The allylation of benzaldehyde with allyl-*n*-tributyltin, catalyzed by Ti(IV)/BINOL complex, was carried out in dichloromethane at -20°C for over 70h (Scheme 15). As the result the homoallylic alcohol was obtained in 95 % enantiomeric excess and 88 % chemical yield.<sup>19</sup>

**Scheme 15.** Ti(IV)/BINOL catalyzed allylation of aldehydes



A modification to Keck's allylation was introduced by Yamamoto and coworkers, who suggested activation of Ti-BINOL catalyst with an additional Lewis acid 4-(trifluoromethyl)phenylboroxin. The reaction was performed on a number of aldehydes with allyltributylstannane and a boroxin (5%)/Ti(O-*i*-Pr)<sub>4</sub> (10%)/BINOL (10%) catalytic complex, in dichloromethane at -20 °C (Scheme 16). With the modification, the reaction times were significantly reduced to about 4 hours, yet enantioselectivity and chemical yields remained high. The enantiomeric excess was as high as 97 % and chemical yields were up to 95 %.<sup>20</sup>

**Scheme 16.** BOROXIN-Ti-BINOL catalyzed allylation of aldehydes.

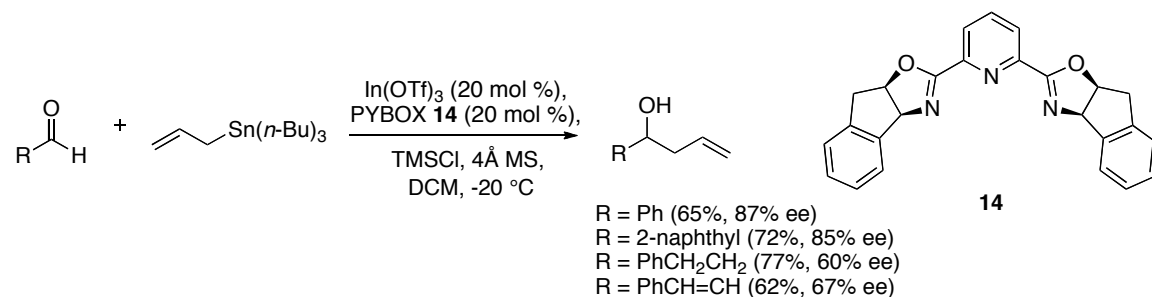


**In(III) catalyzed reactions.** Loh and coworkers introduced the allylation of aldehydes with allyltributylstannane and a chiral indium(III) complex, that was prepared from In(OTf)<sub>3</sub> and the ligand PYBOX **14**. Reaction was performed with addition of 4 Å MS and TMSCl in dichloromethane at -20°C (Scheme 17). The reaction provided moderate to good yields and enantioselectivity (up to 87 % ee<sub>s</sub>) for



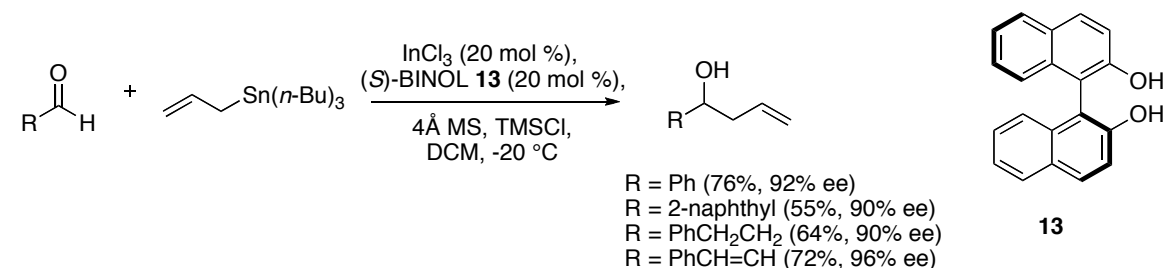
both aromatic and aliphatic aldehydes.<sup>21</sup>

**Scheme 17.** Indium(III)-PYBOX **14** catalyzed allylation of aldehydes.



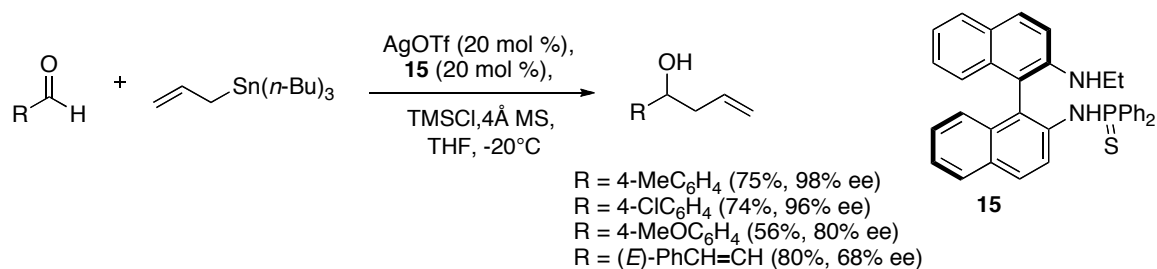
Loh *et al.* later reported another indium(III) complex from (*S*)-BINOL and InCl<sub>3</sub> (Scheme 18). The allylation was performed under the same conditions (with allyltributylstannane and 4 Å MS in dichloromethane at -20°C), and afforded even higher chemical yields and enantioselectivity (up to 96% ee<sub>s</sub>).<sup>22</sup>

**Scheme 18.** Indium(III)-BINOL catalyzed allylation of aldehydes.



**Ag(I) catalyzed reactions.** Shi and coworkers reported the enantioselective allylation of aldehydes with allyltributylstannane under Ag(I) catalysis with chiral binaphthylthiophosphoramidate **15**. The reaction with silver triflate, and chiral ligand **15** in THF at -20°C, provided homoallylic alcohols with up to 93% enantiomeric excess (Scheme 19).<sup>23</sup>

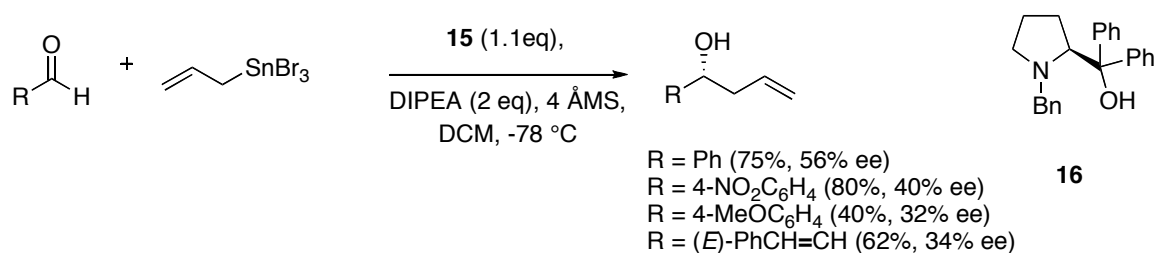
**Scheme 19.** Silver(I) catalyzed allylation.



**2.2.2. Lewis base mediated stoichiometric enantioselective addition of allyltin tribromide.**

**Prolinol catalyzed reactions.** Li *et al.* introduced the use of chiral ligands in conjunction with Lewis bases to promote allylation of aldehydes with allyltin tribromide. The reaction with benzaldehyde and allyltin tribromide, catalyzed by the ligand **16** in combination with DIPEA and 4 Å MS in dichloromethane at -78°C, provided moderate enantiomeric excess (56 % ee<sub>s</sub>) and 75 % chemical yield (Scheme 20).<sup>24</sup>

**Scheme 20.** Prolinol **16**.

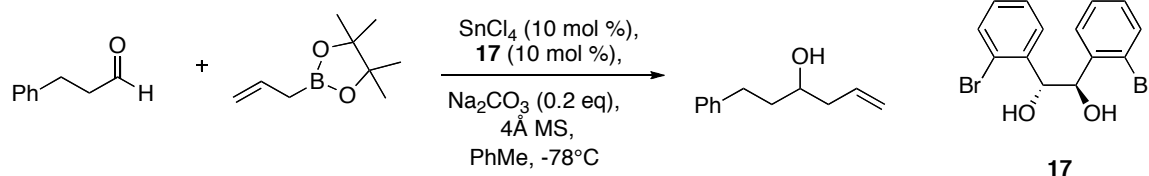


## 2.3. Enantioselective addition of allylic Boranes

### 2.3.1. Lewis acid catalyzed allylations.

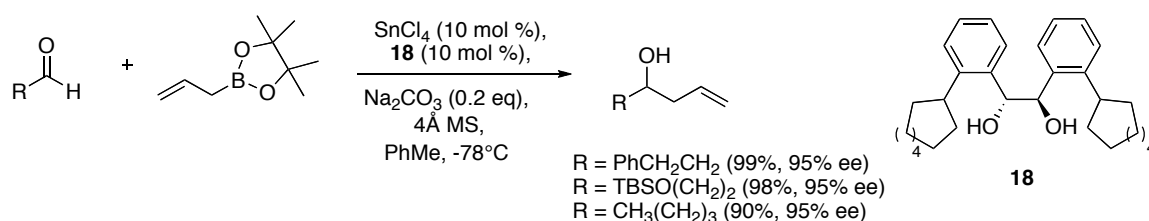
**SnCl<sub>4</sub>/chiral diol catalyzed reactions.** Hall *et al.* developed a number of C<sub>2</sub>-symmetric chiral diols, which in combination with SnCl<sub>4</sub> proved to be very effective in the enantioselective allylation of aldehydes with allylboronic acid pinacol ester. Later Yamamoto and Futatsugi developed a number of different *ortho*-substituted hydrobenzoin-derived diols. The reactions were performed with 10 mol % catalytic amount of SnCl<sub>4</sub> and 10 mol % of diols, in presence of 4Å MS and sodium carbonate in toluene at -78°C (Scheme 21). The most efficient catalysis was with (*R,R*)-**17** diol. Reaction, performed on 3-phenylpropanal, resulted in the formation of alcohol with 77 % enantiomeric excess and in 94 % chemical yield.<sup>25</sup>

**Scheme 21.** Enantioselective allylation of aldehydes catalyzed by chiral diol **17**.



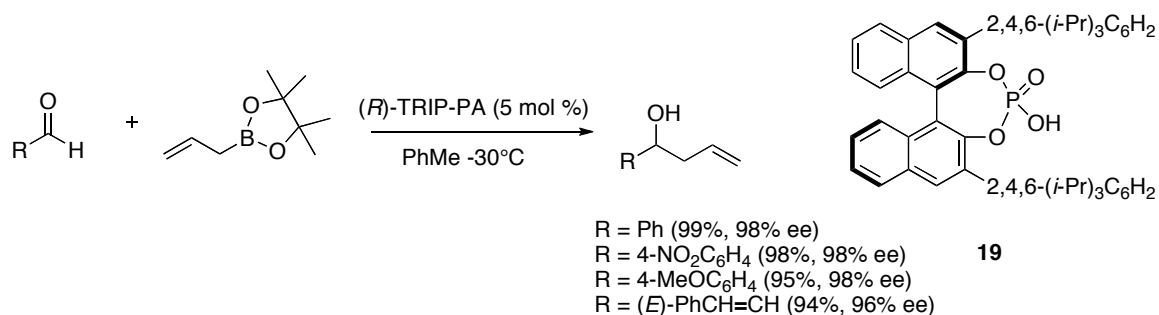
The most efficient chiral diol catalyst (*R,R*)-**18** was developed by Hall *et al.* The reaction was carried out under the same reaction conditions, developed by Yamamoto *et al.* (Scheme 22). The allylation on 3-phenylpropanal, provided the homoallylic alcohol in 99 % chemical yield and with 95 % enantiomeric excess. However the same reaction on aromatic and unsaturated aldehydes gave slightly lower enantioselectivities (71% ee<sub>s</sub> for benzaldehyde).<sup>26</sup>

**Scheme 22.** Tin catalyzed allylation of aldehydes.



**Brønsted acid catalyzed reactions.** Jain and Antilla reported the chiral phosphoric acid-catalyzed allylation of aldehydes with allylboronic acid pinacol ester (Scheme 23). Reaction with phosphoric acid (*R*)-TRIP-PA (*(R)*-**19**) in toluene at  $-30^\circ\text{C}$  was carried out on a number of aldehydes. Catalyst proved to be effective on both electron-rich, electron-poor aromatic aldehydes and  $\alpha,\beta$ -unsaturated aldehydes, with enantiomeric excesses ranging from 96 to 99 %. The catalyst was slightly less effective on aliphatic substrates. For instance allylboration of cyclohexanecarboxaldehyde, resulted in 77 % enantiomeric excess.<sup>27</sup>

**Scheme 23.** Enantioselective allylation of aldehydes catalyzed by (*R*)-TRIP-PA **19**.

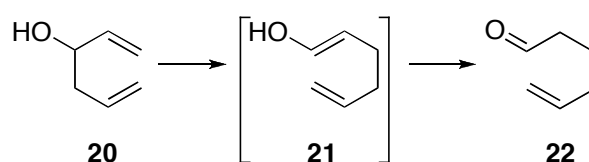


## 2.4. Oxy-Cope Rearrangement

### 2.4.1 Background.

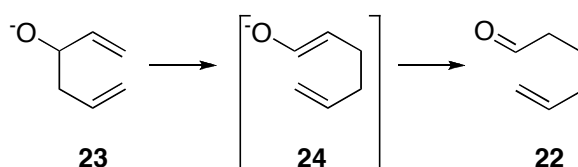
The term 'oxy-Cope' rearrangement was first introduced in 1964 by Berson and Jones, who carried out the classical thermal Cope process on 1,5-hexadien-3-ol **20**. They showed that the presence of the hydroxy substituent on carbon-3 allows the initial formation of an enol **21**, that rapidly tautomerizes to the corresponding carbonyl **22** (Scheme 24). Usually high temperatures (above 200 °C) were required for the process.<sup>28</sup>

**Scheme 24.** Oxy-Cope rearrangement.



Later, the reaction was modified to what is now known as the anionic oxy-Cope rearrangement. When the process was carried out in basic media, the C-3 hydroxy substituent was first deprotonated to **23**, and later converted to the corresponding carbonyl **22** via the enolate intermediate **24** (Scheme 25).<sup>29</sup>

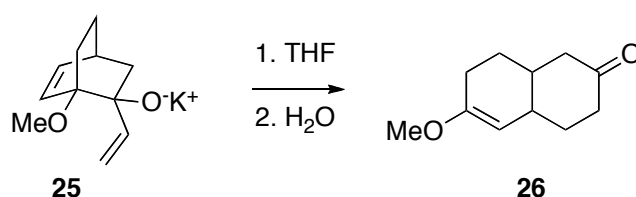
**Scheme 25.** Anionic oxy-Cope rearrangement.



In 1975 Evans and Golub reported a significant increase in rate accelerations (up to  $10^{17}$ ). It was accomplished by converting the alcohols to the corresponding

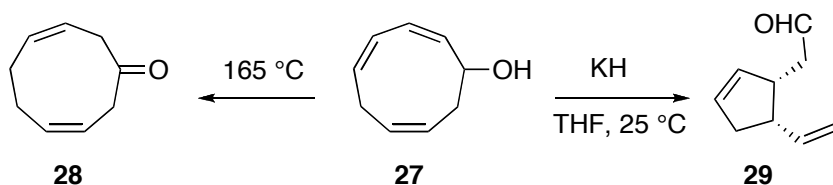
potassium alkoxides **25**, which then underwent the very rapid rearrangement (half-life = 1.4 min) (Scheme 26). The process was carried out in presence of a crown ether in THF. Interestingly, under the same conditions, no reaction was observed with the Li or MgBr salts, and Na salt reacted much slower (half-life = 1.2 h).<sup>30</sup>

**Scheme 26.** Anionic oxy-Cope rearrangement of potassium alkoxide.



In some thermal oxy-Cope rearrangements a number of competing reactions were observed. For instance, when alcohol **27** is heated to 165 °C, it undergoes a [1,5]-hydrogen migration to provide a ketone **28**. However, when **27** is treated with potassium hydride, the oxy-Cope rearrangement is strongly accelerated, and the [1,5]-sigmatropic shift is not observed (Scheme 27).<sup>31</sup>

**Scheme 27.** Competing reactions.

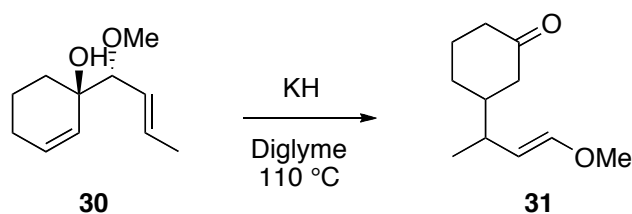


#### 2.4.2 Transfer reactions on cyclic frameworks

An interesting and very functional application of the anionic oxy-Cope rearrangement is in the case of the migration of groups around the periphery of rings

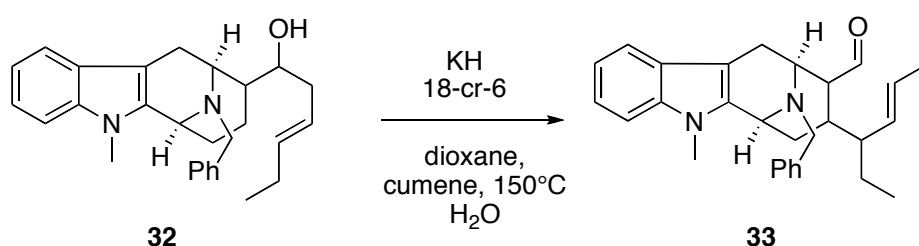
of different sizes and types. For example, Evans and Nelson reported a migration of alkenyl group on alcohol **30** with potassium hydride in diglyme at 110 °C (Scheme 28). The corresponding ketone **31** was obtained in a very high yield (96 %).<sup>32</sup>

**Scheme 28.** Migration of alkenyl group via anionic oxy-Cope.



A different example of the transfer application was reported by Fu and Cook. Alcohol **32** underwent the anionic oxy-Cope rearrangement in the presence of KH and a crown-ether in dioxane and cumene at 150 °C to provide the aldehyde **33** in 88 % yield (Scheme 29). Due to the hindered nature of alcohol **32**, higher temperatures were required for the rearrangement to occur.<sup>33</sup>

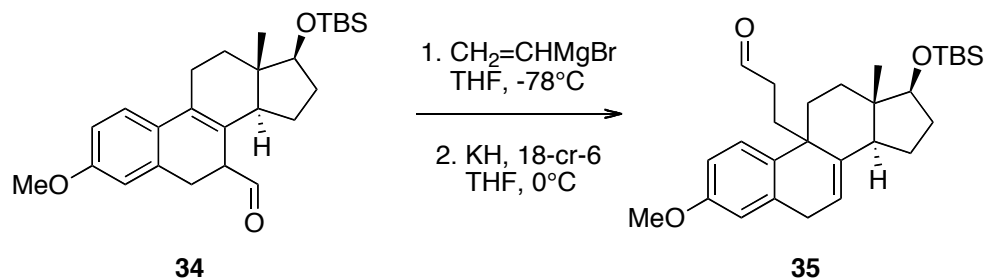
**Scheme 29.** Migration of the alkenyl group via anionic oxy-Cope.



A further interesting case was demonstrated by Bojack *et al.* He incorporated the anionic oxy-Cope rearrangement as one of the key steps in his synthesis of estratetraenes. The addition of vinyl magnesium bromide to aldehyde **34** afforded two diastereoisomeric allylic alcohols in 66 % combined yields. Upon treatment with potassium hydride/18-crown-6 in THF at 0 °C for two hours, both compounds

subsequently converged to **35** (85 % yield) (Scheme 30).<sup>34</sup>

**Scheme 30.** Key reactions of Bojack's synthesis of estratetraenes.



### 3. Objectives of the project

The main objective of this work was to explore a possibility of a new route for an enantioselective synthesis of 6–6–6 condensed ring system from a bicyclic unsaturated aldehyde. The key idea for this novel synthesis consisted in enantioselective allylation of a  $\alpha,\beta$ -unsaturated bicyclic aldehyde followed by the oxy-Cope rearrangement with subsequent elaboration of the formed intermediate.

In order to accomplish the overall objective several tasks were set:

- to carry out enantioselective allylation of the  $\alpha,\beta$ -unsaturated bicyclic aldehyde and ketone under a variety of reaction conditions and evaluate these methodologies according to the highest enantioselectivity and chemical yields;
- to perform the oxy-Cope rearrangement on the resulting bicyclic alcohol, and to observe if the optical purity would be conserved;
- finally, to prepare a tricyclic framework from the resulting oxy-Cope product.

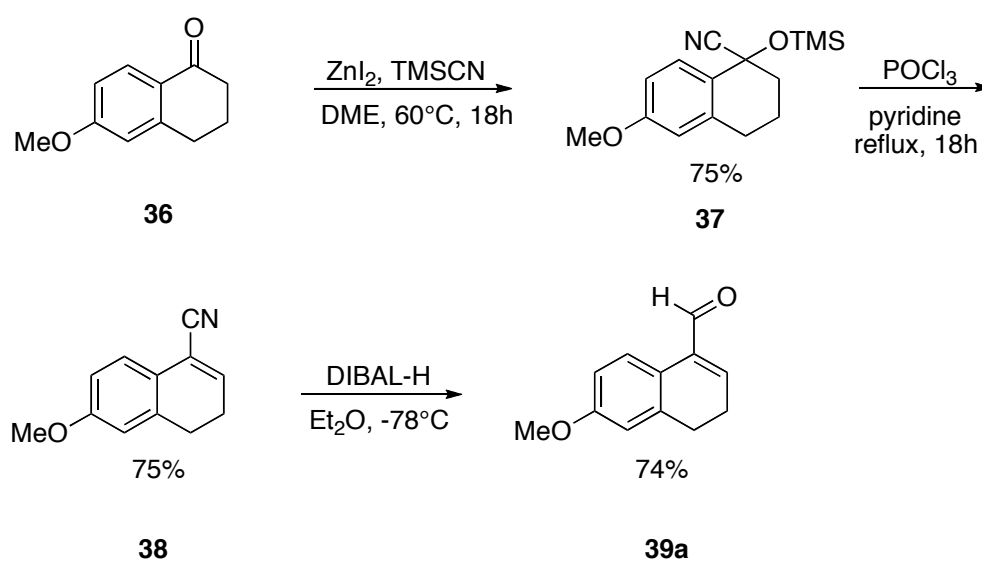


## 4. Results and Discussion

### 4.1. Synthesis of the starting material.

The starting material was synthesized according to the procedure, previously described in the literature.<sup>35</sup> The reaction of commercially available 6-methoxytetralone **36** with trimethylsilyl cyanide and zinc iodide in DME at 60 °C for 18 hours afforded the nitrile **37** in 75 % yield (Scheme 31). Successive elimination with phosphoryl chloride in pyridine at reflux overnight, resulted in the formation of the  $\alpha,\beta$ -unsaturated nitrile **38** in 75 % yield. The final reduction with DIBAL-H in Et<sub>2</sub>O at -78 °C provided the  $\alpha,\beta$ -unsaturated aldehyde **39a** in 74 % yield.<sup>36</sup> The  $\alpha,\beta$ -unsaturated ketone **39b**, as the second starting material, was obtained from the lab.

**Scheme 31.** Synthesis of the starting material.



## 4.2. Enantioselective allylation of $\alpha,\beta$ -unsaturated aldehyde **39a**.

Enantioselective allylations of **39a** were carried out under different reaction condition (the used chiral catalysts or chiral ligands are displayed in Fig. 1) with several allylating agents (Fig. 2). The results are summarized in Tables 2. The racemic alcohol **44a** was prepared by the reaction of **39a** with allylmagnesium bromide.

### 4.2.1 Brønsted acid catalyzed allylation.

**R-TRIP-PA.** The Brønsted acid catalyzed allylation was performed according to the procedure of Jain and Antilla. The reaction with the  $\alpha,\beta$ -unsaturated aldehyde **39a**, allylboronic acid pinacol ester **40b** and 5 mol % phosphoric acid (*S*)-TRIP-PA **19** was carried out in toluene at -30 °C for 18 hours.<sup>27</sup> As the result, the allylic alcohol **44a** was obtained in 30 % yield and 68 % enantiomeric excess.

### 4.2.2 Lewis acid catalyzed allylation.

**Dibromo-BINOL-catalyzed allylation.** The procedure, introduced by Sha Lou was used for allylation of the  $\alpha,\beta$ -unsaturated aldehyde **39a** with dibromo-BINOL **25**. The reaction mixture with aldehyde **39a**, allylboronic acid pinacol ester **40b** and 10 mol % (*R*)-dibromo-BINOL **25** was allowed to react in toluene/ $\alpha,\alpha,\alpha$ -trifluorotoluene (3/1) at -35 °C for 18 hours.<sup>37</sup> As the result, the homoallylic alcohol **44a** was obtained in 70 % NMR yield, however, the product was racemic.

**Ag(I) catalyzed allylation.** The next attempts were based on the work of Yamamoto and coworkers, who described Ag(I) catalyzed allylations. In the first procedure, the  $\alpha,\beta$ -unsaturated aldehyde **39a** was treated with allyltrimethoxysilane

**40c**, catalytic amount of KF, 18-crown-6, 5 mol % (*S*)-BINAP **1** and 5 mol % AgOTf. The reaction was left in THF at -20 °C for 18 hours.<sup>4</sup> As a result, the allylated alcohol **44a** was obtained in 88 % NMR yield and with 89 % ee<sub>s</sub>.

The second procedure was based on the catalysis with Ag(I)-DIFLUORPHOS complex. The  $\alpha,\beta$ -unsaturated aldehyde **39a** was allowed to react with allyltrimethoxysilane **40c**, 5 mol % (*S*)-DIFLUORPHOS **26** and 5 mol % AgOTf. The reaction was carried out in THF/MeOH at -78 °C for 18 hours. However, the reaction did not take place and no product was obtained.<sup>38</sup>

**Ti(IV) catalyzed reaction.** The next attempted procedure was titanium-BINOL mediated allylation, developed by Keck *et. al.*. The  $\alpha,\beta$ -unsaturated aldehyde **39a** was treated with allyl(tri-*n*-butyl)stannane **40e**, Ti(O-*i*-Pr)<sub>4</sub> (1 eq) and (*S*)-BINOL **13** (1 eq) in dichloromethane at -20 °C for 168 hours. As the result, the allylic alcohol **44a** was obtained in 26 % yield and 95 % enantiomeric excess.<sup>19</sup>

Motivated by such high enantiomeric excess, but attempting to increase the chemical yield, we turned to Hanawa's *et.al.* work, who were able to achieve high ee<sub>s</sub> and chemical yields by applying the chiral bis-Ti<sup>IV</sup> oxide **27** catalytic complex. In order to prepare the chiral bis-Ti<sup>IV</sup> oxide, Ti(O-*i*-Pr)<sub>4</sub>, TiCl<sub>4</sub> and Ag<sub>2</sub>O were mixed with (*S*)-BINOL **13** in dichloromethane. The catalytic mixture was then added to the  $\alpha,\beta$ -unsaturated aldehyde **39a**, followed by addition of allyl(tri-*n*-butyl)stannane **40e**.<sup>39</sup> Unfortunately, after 18 hours of reaction time, no product was formed.

### 4.2.3 Lewis base catalyzed allylation.

***N*-Oxides catalyzed allylation.** Next, we evaluated the chiral bipyridine *N,N'*-dioxides (**8a-8d**) with a bis(tetrahydroisoquinoline) framework, developed by Kotora and coworkers.<sup>13</sup>

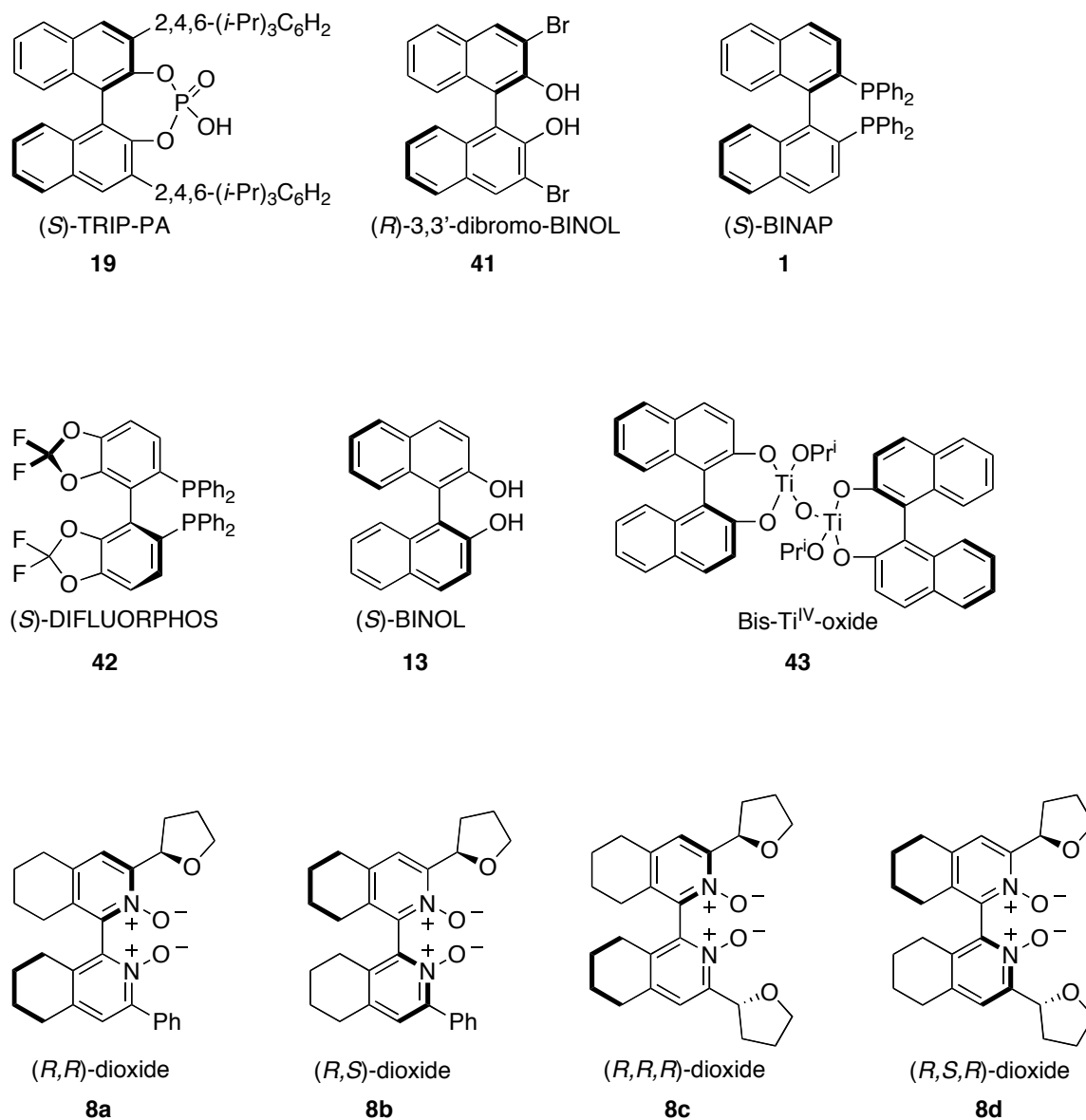
First of all, (*R,R*)-*N,N'*-dioxide **8a** (5 mol %) was allowed to react with the

$\alpha,\beta$ -unsaturated aldehyde **39a** and allyltrichlorosilane **40d** in presence of DIPEA. The reaction mixture was carried out in THF at -40 °C for 18 hours. As the result, the allylated alcohol **44a** was obtained in 90 % NMR yield, with 68 % enantiomeric excess. The reaction was repeated in dichloromethane at -40 °C for 18 hours, using 1 mol % of (*R,R*)-*N,N'*-dioxide **8a**. The allylated alcohol **44a** was obtained in 70 % NMR yield, with 66 % enantiomeric excess. The final trial was carried out in toluene at -40 °C for 18 hours, using 1 mol % of (*R,R*)-*N,N'*-dioxide **8a**. However, the reaction did not take place and no product was obtained.

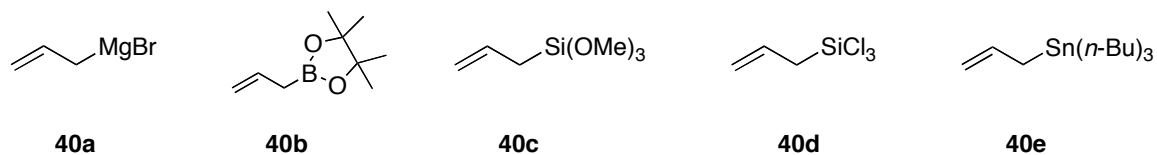
The allylation was also attempted with 5 mol % (*R,S*)-*N,N'*-dioxide **8b** and (*R,S,R*)-*N,N'*-dioxide **8d** in THF, under the same reaction conditions. The allylated alcohol **44a** was obtained in 90 and 68 % NMR yields and with 60 and 22 % enantiomeric excesses, representatively. However, when (*R,R,R*)-*N,N'*-dioxide **8c** was used under the same conditions, reaction did not proceed and no product was obtained.

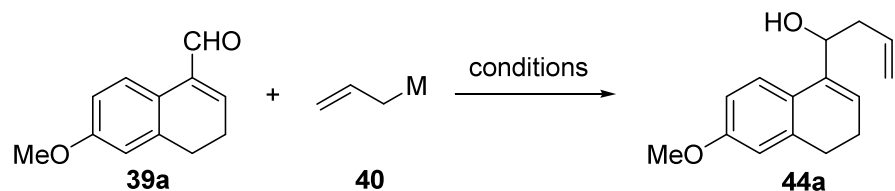
It has been shown that allylation of aromatic and  $\alpha,\beta$ -unsaturated aldehydes with allyltrichlorosilane catalyzed by the (*R,R*)-*N,N'*-dioxide **8a** in THF give predominantly products with *R* configuration, whereas those catalyzed by and the (*R,S*)-*N,N'*-dioxide **8b** give predominantly products with *S* configuration.<sup>13,14</sup> In view of that configurations of the newly prepared homoallylic alcohols were estimated accordingly (Table 2).

**Figure 1.** Catalysts and ligands used in enantioselective allylations of **39**.



**Figure 2.** Allylating agents.



**Table 2.** Enantioselective allylation of the  $\alpha,\beta$ -unsaturated aldehyde **39a**.

Allylating agent	Catalyst	(mol %)	Solvent	T (°C)	R. t. (h)	Yield (%)	ee (%) <sup>c</sup>
<b>40a</b>			THF	-78	18	74	racemic
<b>40b</b>	( <i>S</i> )-TRIP-PA ( <b>19</b> )	5	toluene	-30	18	30	68 ( <i>S</i> )
<b>40b</b>	( <i>R</i> )-3,3'-dibromo-BINOL ( <b>41</b> )	10	Tol/PhCF <sub>3</sub> (3/1)	-35	18	70 <sup>b</sup>	0
<b>40c</b>	AgOTf ( <i>S</i> )-BINAP ( <b>1</b> ), KF, Crown-ether	5 5	THF	-20	4	88 <sup>b</sup>	89 ( <i>R</i> )
<b>40c</b>	AgOTf ( <i>S</i> )-DIFLUORPHOS ( <b>42</b> )	5 5	MeOH/THF	-78	18	0	0
<b>40d</b>	( <i>R,R</i> )-dioxide ( <b>8a</b> )	5	THF	-40	18	90 <sup>b</sup>	68 ( <i>R</i> )
<b>40d</b>	( <i>R,R</i> )-dioxide ( <b>8a</b> )	1	DCM	-40	18	55 <sup>b</sup>	66 ( <i>S</i> )
<b>40d</b>	( <i>R,R</i> )-dioxide ( <b>8a</b> )	1	toluene	-40	18	0	0
<b>40d</b>	( <i>R,S</i> )-dioxide ( <b>8b</b> )	5	THF	-40	18	90 <sup>b</sup>	60 ( <i>S</i> )
<b>40d</b>	( <i>R,R,R</i> )-dioxide ( <b>8c</b> )	5	THF	-40	18	0	0
<b>40d</b>	( <i>R,S,R</i> )-dioxide ( <b>8d</b> )	5	THF	-40	18	68 <sup>b</sup>	22 ( <i>S</i> )
<b>40e</b>	Ti( <i>O-i</i> -Pr) <sub>4</sub> , TiCl <sub>4</sub> , Ag <sub>2</sub> O ( <i>S</i> )-BINOL ( <b>13</b> )	10 10 10 10	DCM	0	18	0	0
<b>40e</b>	Ti( <i>O-i</i> -Pr) <sub>4</sub> ( <i>S</i> )-BINOL ( <b>13</b> )	100 100	DCM	-20	168 (7 days)	26	95 ( <i>S</i> )

<sup>a</sup> Isolated yields unless otherwise mentioned.<sup>b</sup> <sup>1</sup>H NMR yield; <sup>c</sup>GC charts are in the appendix

### 4.3. Enantioselective Allylation of $\alpha,\beta$ -unsaturated ketone **39b**.

Enantioselective allylations of **39b** were carried out under different reaction condition (the used chiral catalysts or chiral ligands are displayed in Fig. 1) with several allylating agents (Fig. 2). The results are summarized in Table 3. The racemic alcohol **44b** was prepared by the reaction of **39b** with allylmagnesium bromide.

#### 4.3.1 Lewis-acid catalyzed allylation.

**Dibromo-BINOL catalyzed.** The dibromo-BINOL **41** catalyzed allylation was also attempted on the  $\alpha,\beta$ -unsaturated ketone **39b**. The ketone **39b** was treated with allylboronic acid pinacol ester **40b** and 10 mol % (*R*)-dibromo-BINOL **41**. The reaction was carried out in toluene/PhCF<sub>3</sub> (3/1) at -35 °C for 18 hours.<sup>37</sup> However, the reaction did not take place and no product was obtained.

**Ag(I) catalyzed allylation.** Next, the Ag(I) catalyzed allylations, described by Yamamoto were attempted. First, the  $\alpha,\beta$ -unsaturated ketone **39b** was treated with allyltrimethoxysilane **40c**, catalytic amount of KF, 18-crown-6, 5 mol % (*S*)-BINAP **1** and 5 mol % AgOTf in THF at -20 °C for 4 hours.<sup>4</sup> However, the reaction did not work and no product was obtained.

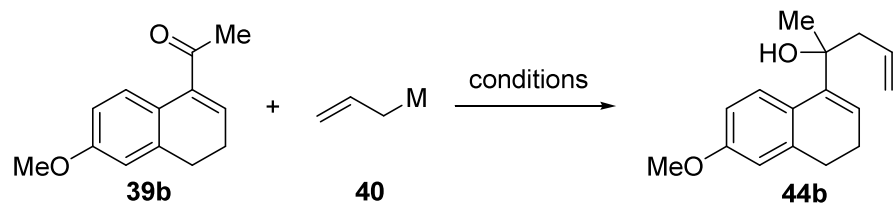
Afterward, the  $\alpha,\beta$ -unsaturated ketone **39b** was treated with allyltrimethoxysilane **40c**, 5 mol % (*S*)-DIFLUORPHOS **42** and 5 mol % AgOTf in THF/MeOH at -78 °C for 18 hours. As the result, the tertiary allylic alcohol **44b** was obtained in 10 % NMR yield and with 88 % enantiomeric excess.<sup>38</sup> In order to increase the chemical yield, the amount of catalytic complex was increased to 15 mol %, which afforded the tertiary allylic alcohol **44b** in 90 % NMR yield and with 92 % ee<sub>s</sub>.

**Ti (IV) catalyzed reaction.** Finally the Keck's allylation, that allowed such high enantioselectivity on the aldehyde, was also evaluated on the ketone **39b**. The mixture of  $\alpha,\beta$ -unsaturated ketone **39b**, allyl(tri-*n*-butyl)stannane **40e**, Ti(O-*i*-Pr)<sub>4</sub> (1 eq) and (*S*)-BINOL **13** (1 eq) was allowed to react in dichloromethane at -20 °C for 168 hours. However, the reaction did not work and no product was obtained.<sup>19</sup>

It has been shown that allylation of aromatic and  $\alpha,\beta$ -unsaturated ketones with allyltrimethoxysilane **40c** catalyzed by the Ag(I)/(*R*)-DIFLUORPHOS **42** in THF/MeOH give predominantly products with *R* configuration, whereas those catalyzed by and the Ag(I)/(*S*)-DIFLUORPHOS **42** give predominantly products with *S* configuration.<sup>38</sup> In view of that configurations of the newly prepared alcohols were estimated accordingly (Table 3).



**Table 3.** Enantioselective allylations of the  $\alpha,\beta$ -unsaturated ketone **39b**.



Allylating agent	Catalyst	(mol %)	Solvent	T (°C)	R. t. (h)	Yield (%)	ee (%)
<b>40a</b>			THF	-78	18	74	racemic
<b>40b</b>	( <i>R</i> )-3,3'-dibromo-BINOL ( <b>41</b> )	10	Tol/PhCF <sub>3</sub> (3/1)	-35	18	0	0
<b>40c</b>	AgOTf ( <i>S</i> )-BINAP ( <b>1</b> ) KF, Crown-ether	5 5	THF	-20	4	0	0
<b>40c</b>	AgOTf ( <i>S</i> )-DIFLUORPHOS ( <b>42</b> )	5 5	MeOH/THF	-78	18	10 <sup>b</sup>	88 ( <i>S</i> )
<b>40c</b>	AgOTf ( <i>S</i> )- DIFLUORPHOS ( <b>42</b> )	15 15	MeOH/THF	-78	18	90 <sup>b</sup>	92 ( <i>S</i> )
<b>40e</b>	Ti(O- <i>i</i> -Pr) <sub>4</sub> ( <i>S</i> )-BINOL ( <b>13</b> )	100 100	DCM	-20	168 (7 days)	0	0

<sup>a</sup> Isolated yields unless otherwise mentioned.

<sup>b</sup> <sup>1</sup>H NMR yield.

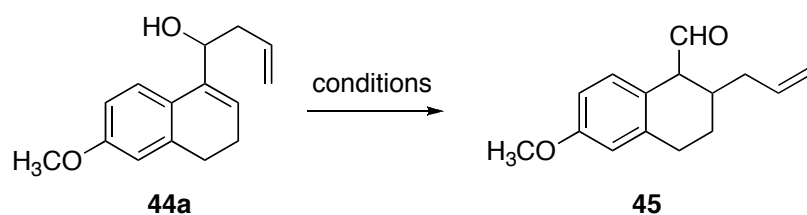
<sup>c</sup> GC charts are in the appendix.

#### 4.4. Oxy-Cope rearrangement.

The next aim of the work was to carry out the racemic oxy-Cope rearrangement on the obtained homoallylic alcohol **44a**. Several procedures for the oxy-Cope rearrangement of the homoallyl alcohol **44a** were evaluated (Table 4).

Initially, potassium hydride induced rearrangement was attempted under several conditions. Firstly, the alcohol **44a** was treated with potassium hydride and 18-crown-6-ether in THF. The reaction mixture was heated to 60 °C and was left for 78 hours. The reaction progress was monitored by TLC; however, no product formation was observed.<sup>40</sup>

**Table 4.** Oxy-Cope rearrangement conditions.



Entry	Conditions	Solvent	T (°C)	t (h)	Yield (%) <sup>a</sup>
1	KH (1 eq), 18-cr-6	THF	60	78	0
2	KH (1 eq), 18-cr-6	diglyme	25	18	0
3	P <sub>4</sub> - <i>t</i> -Bu <b>30</b> (1.1 eq)	THF/hexanes 1/1	0 to 20	18	0
4	KH (1 eq), 18-cr-6, MW	THF	180	0.33	80

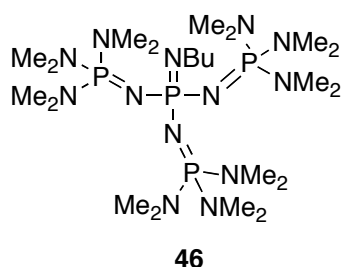
<sup>a</sup> Isolated yields.

Afterward, the reaction was also repeated in diglyme at 25 °C (Entry 2). The reaction progress was again monitored by TLC; however, again no product formation was observed.<sup>40</sup>

It was then decided to attempt the rearrangement under stronger basic conditions, based on the work of Mamadi and Hartley, who reported the phosphazene

super-base **46** (Figure 3) mediated oxy-Cope rearrangement. The allylic alcohol **44a** was mixed with the super-base **46** in THF/Hexane (1/1). The reaction was allowed to heat from 0 °C to room temperature, and left overnight (Entry 3). However, the reaction did not take place, and no product was obtained.<sup>41</sup> Heating the reaction to 50 °C (for 18 h), and then to 100 °C (18 h) seemed to have no effect on the course of the reaction. TLC monitoring showed the presence of the starting alcohol **44a** only.

**Figure 3.** Phosphazene super-base **46**.

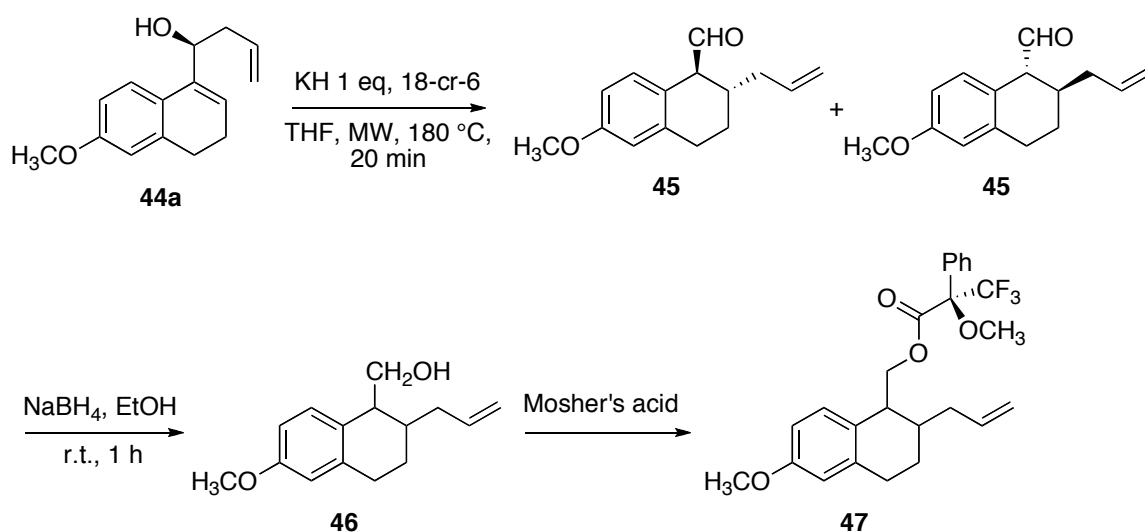


Finally, inspired by the successful reports on the microwave enhanced reactions, we decided to attempt the oxy-Cope rearrangement in the microwave. The mixture of the allylic alcohol **44a**, potassium hydride and crown ether in THF was allowed to react at 180 °C in the microwave for 20 minutes (Entry 4).<sup>42</sup> The reaction was a success, providing the bicyclic aldehyde **45** in 80 % yield.

The next step was to carry out the rearrangement on the chiral alcohol **44a** (Scheme 32). The most optically pure alcohol **44a** (95 % ee) was selected. The purpose was to observe, if the optical purity is conserved during the oxy-Cope rearrangement. However, after completion of the reaction according to the optimized microwave procedure, it was observed that the optical purity was partially lost. It was not possible to determine the ee<sub>s</sub> by measurement on either GC or HPLC with chiral stationary phase, therefore the aldehyde **45** was reduced to alcohol **46**, which was then

allowed to react with Mosher's acid. The resulting Mosher's ester **47** was used to determine the optical purity. The enantiomeric excess was reduced from 95 % to 20 % ee<sub>s</sub>. The absolute configuration of the aldehyde **45** is not apparent. However, relative stereochemistry is assumed to be *trans* due to the expected higher thermodynamic stability.

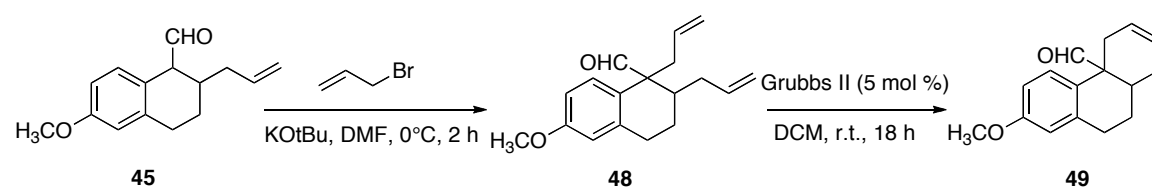
**Scheme 32.** Oxy-Cope rearrangement on the chiral alcohol **44a**.



#### 4.5. Synthesis of Tricyclic Framework.

The bicyclic aldehyde **45**, obtained from the Oxy-Cope rearrangement, was further used for the synthesis of the tricyclic framework **49**. The first step was the  $\alpha$ -allylation of the aldehyde **45** with allyl bromide, in the presence of potassium *tert*-butoxide base in DMF (Scheme 33).<sup>43</sup> The reaction was completed after 2 hours, resulting in the formation of the aldehyde **48** in 73 % yield. The succeeding metathesis was performed using the Grubbs II catalyst in dichloromethane.<sup>44</sup> As a result, the tricyclic framework **49** was obtained in 86 % yield.

**Scheme 33.** Synthesis of the tricyclic framework.

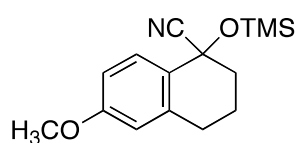


## 5. Experimental Section

**General.** All solvents unless otherwise stated were used as obtained. THF and Et<sub>2</sub>O were distilled from LiAlH<sub>4</sub>, dichloromethane from CaH<sub>2</sub>, toluene from sodium benzophenone ketyl. All other reagents were obtained from commercial sources. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Varian UNITY 400 (<sup>1</sup>H at 400 MHz, <sup>13</sup>C at 100.6 MHz) and Varian UNITY 300 (<sup>1</sup>H at 300 MHz, <sup>13</sup>C at 75 MHz) as solutions in CDCl<sub>3</sub> or C<sub>6</sub>D<sub>6</sub> at 25 °C. Chemical shifts are given in δ-scale, coupling constants J are given in Hz. Mass spectra were recorded on a ZAB-SEQ (VGAAnalytical) instrument. Infrared spectra were recorded on a Bruker IFS 55 spectrometer as THF solutions and are reported in wave numbers (cm<sup>-1</sup>). Fluka 60 silica gel was used for flash chromatography. TLC was performed on silica gel 60 F254-coated aluminum sheets (Merck). All reactions were carried out under an argon atmosphere using flasks.

### 5.1. Synthesis of the starting material

#### 1-Cyano-1-trimethylsilyloxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (37).



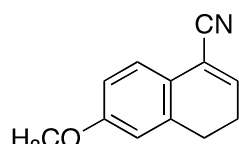
6-Methoxytetralone **36** (9.00 g, 51 mmol) was dissolved in dimethoxyethane under argon atmosphere for 30 minutes. Then ZnI<sub>2</sub> (0.41 g, 0.12 mmol) was added. The reaction mixture was allowed to heat to 60 °C, and TMSCN (6.5 mL, 51.94 mmol) was added, and then the reaction mixture was left overnight at 60 °C. The solution of 5% NaHCO<sub>3</sub> (200 mL) was added dropwise to quench the reaction, followed by extraction with dichloromethane (3×30 mL). The combined organic fractions were dried over anhydrous MgSO<sub>4</sub>. Volatiles were removed under

reduced pressure to yield 10.45 g (75 %) of the title compound as a colorless oil. ( $R_f$  ( $\text{CH}_2\text{Cl}_2$ ) = 0.4.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.3-7.4 (m, 1H), 6.8-6.9 (m, 1H), 6.5-6.6 (m, 1H), 3.8 (m, 3H), 2.7-2.8 (m, 2H), 1.9-2.2 (m, 4H), 0.2 (m, 9H);

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  0 (TMS), 18.65 ( $\text{CH}_2$ ), 28.72 ( $\text{CH}_2$ ), 37.94 ( $\text{CH}_2$ ), 55.23 ( $\text{OCH}_3$ ), 69.58 ( $\text{CR}_4$ ), 112.90 (Ar), 113.50 (Ar), 122.27 (Ar), 128.17 (Ar), 129.53 (Ar), 137.75 (Ar), 159.94 (Ar). Spectral characteristics were in agreement with the previously reported data.<sup>35</sup>

### 1-Cyano-6-methoxy-3,4-dihydronaphthalene (38).



1-Cyano-1-trimethylsilyloxy-6-methoxy-1,2,3,4-

tetrahydronaphthalene **37** (10g , 36 mmol) was dissolved in pyridine (50 mL), and  $\text{POCl}_3$  (12 mL, 134 mmol) was added. The reaction mixture was left overnight under reflux. Water (300 mL) was added dropwise to quench the reaction, followed by extraction with dichloromethane (3 $\times$ 30 mL). The combined organic fractions were washed with 5% HCl (50 mL), and then dried over anhydrous  $\text{MgSO}_4$ . Volatiles were removed under reduced pressure to yield 5 g (75 %) of the title compound as a colorless oil.

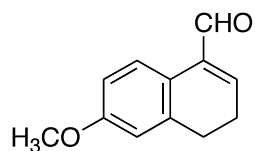
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.3-7.4 (m, 1H), 6.6-6.8 (m, 3H), 3.8 (m, 3H), 2.7-2.9 (m, 2H), 2.4-2.5 (m, 2H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  23.51 ( $\text{CH}_2$ ), 26.54 ( $\text{CH}_2$ ), 55.29 ( $\text{OCH}_3$ ), 111.54 (Ar), 113.77 (Ar), 114.20 (Ar), 117.28 ( $\text{C}=\text{C}$ ), 121.76 (Ar), 126.05 (Ar), 136.02 (Ar), 140.81 ( $\text{C}=\text{C}$ ), 160.10 (Ar).

$R_f$  ( $\text{CH}_2\text{Cl}_2$ ) = 0.6.

Spectral characteristics were in agreement with the previously reported data.<sup>35</sup>

**1-Formyl-6-methoxy-3,4-dihydronaphthalene (39a).**



1-Cyano-6-methoxy-3,4-dihydronaphthalene **38** (5.00 g, 27

mmol) was dissolved in Et<sub>2</sub>O (150 mL) at -78 °C. The solution was left to stir under argon for 30 min, followed by dropwise addition of DIBAL-H (42 mL, 42 mmol). The reaction mixture was left for 4 hours to heat up to room temperature. Water (200 mL) was added dropwise to quench the reaction, followed by extraction with dichloromethane (3×30 mL). The organic fractions were dried over anhydrous MgSO<sub>4</sub>. Volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography in dichloromethane. The compound was then distilled at 120° C and 2.0 mbar pressure to yield 3.7 g (74 %) of the title compound as a colorless oil.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.6-9.7 (m, 1H), 8.1-8.2 (m, 1H), 6.9-7.0 (m, 1H), 6.7-6.9 (m, 2H), 3.8 (m, 3H), 1.9-2.2 (m, 4H), 2.7-2.8 (m, 2H), 2.5-2.7 (m, 2H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 24.17 (CH<sub>2</sub>), 27.37 (ArCH<sub>2</sub>), 55.13 (OCH<sub>3</sub>), 110.99 (Ar), 113.78 (Ar), 122.29 (Ar), 127.12 (Ar), 137.66 (Ar), 137.73 (C=CH), 150.57 (C=CH) 159.31 (Ar), 192.72 (CHO).

R<sub>f</sub> (CH<sub>2</sub>Cl<sub>2</sub>) = 0.5.

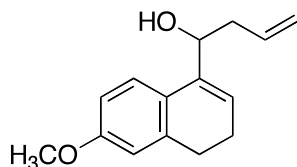
Spectral characteristics were in agreement with the previously reported data.<sup>36</sup>



## 5.2. Allylations

### 5.2.1. Allylations of $\alpha,\beta$ -unsaturated aldehyde 39a

#### 1-(6-Methoxy-3,4-dihydronaphthalen-1-yl)but-3-en-1-ol (44a).



**Racemic synthesis.** 1-Formyl-6-methoxy-3,4-dihydronaphthalene (2.0 g, 10.6 mmol) was dissolved in distilled THF and left to cool under argon in dry ice. Allylmagnesium bromide (19.0 mL, 18.8 mmol) was added, and the reaction mixture was left for 5h. Water was added dropwise to quench the reaction mixture, followed by extraction with dichloromethane (3×30 mL). The organic fractions were washed with 5% HCl (50 mL). Volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel in dichloromethane. The compound was then distilled at 140° C and 2.0 mbar pressure to yield 1.77 g (73 %) of the title compound as a colorless oil.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.3-7.4 (m, 1H), 6.6-6.7 (m, 2H), 5.9-6.0 (m, 1H), 5.7-5.9 (m, 1H), 5.0-5.2 (m, 2H), 4.6-4.7 (m, 1H), 3.7 (m, 3H), 2.6-2.8 (m, 2H), 2.5-2.6 (m, 2H), 2.2-2.4 (m, 2H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  22.74 ( $\text{CH}_2$ ), 28.77 ( $\text{ArCH}_2$ ), 40.83 ( $\text{CH}_2$ ), 55.18 ( $\text{OCH}_3$ ), 70.78 ( $\text{CHOH}$ ), 110.90 (Ar), 114.02 (Ar), 117.80 ( $\text{C}=\text{CH}$ ), 122.37 (Ar), 123.99 ( $\text{C}=\text{CH}$ ), 126.27 (Ar), 134.97 (Ar), 138.16 ( $\text{C}=\text{CH}$ ), 138.82 ( $\text{C}=\text{CH}$ ), 158.41 (Ar).

IR (KBr)  $\nu$  3346, 3069, 3031, 2998, 2977, 2938, 2908, 2884, 2833, 1640, 1607, 1565, 1497, 1467, 1428, 1323, 1302, 1284, 1248, 1144, 1042, 1021, 919, 833.

HRMS (EI+) calcd. for  $\text{C}_{15}\text{H}_{18}\text{O}_2\text{Na}$  253.11971, found 253.11990.

$R_f(\text{CH}_2\text{Cl}_2) = 0.3$ .

Optical purity: racemic.

$E_e$ s were determined by GC (HP-Chiral  $\beta$  column, 30m  $\times$  0.25 mm, oven: 80° C for 1 min, then 1° C/min to 160 °C, 5 min):  $t_1 = 55.32$  min (50.8%) ,  $t_2 = 56.05$  min (49.2%).

**(S)-TRIP-PA catalyzed reaction.** (S)-TRIP-PA (0.024 g, 0.03 mmol) and 1-formyl-6-methoxy-3,4-dihydronaphthalene (0.108 g, 0.52 mmol) were dissolved in dry toluene (4 mL) under argon atmosphere. The reaction mixture was then cooled to -30 °C followed by the dropwise addition of allylboronic acid pinacol ester (0.106 g, 0.63 mmol) over 30 seconds. The mixture was stirred overnight at this temperature. The reaction mixture was then quenched by vacuum column chromatography in dichloromethane, resulting in 0.042 g (35 %) of the title compound as a colorless oil.<sup>27</sup>

Optical purity: 69%  $ee_s$ .

$E_e$ s were determined by GC (HP-Chiral  $\beta$  column, 30m  $\times$  0.25 mm, oven: 80° C for 1 min, then 1° C/min to 160 °C, 5 min):  $t_1 = 56.36$  min (84.6%) ,  $t_2 = 57.07$  min (15.4%).

**Ag(I)/BINAP catalyzed reaction.** A mixture of AgOTf (0.064 g, 0.25 mmol), (S)-BINAP (0.155 g, 0.25 mmol), KF (0.014 g, 0.25 mmol), and 18-crown-6 (0.060 g, 0.23 mmol) was dissolved in dry THF (2 mL) under argon atmosphere and with direct light excluded, and cooled to - 20 °C. To the resulting solution 1-formyl-6-methoxy-3,4-dihydronaphthalene (0.048 g, 0.25 mmol) and allyltrimethoxysilane (126  $\mu\text{L}$ , 0.75 mmol) were added successively at -20 °C. The mixture was stirred for 18 h at this

temperature. The solution of 1M HCl (5 mL) was added dropwise to quench the reaction, followed by extraction with dichloromethane (3×5 mL). The combined organic fractions were dried over anhydrous MgSO<sub>4</sub>. Volatiles were removed under reduced pressure.<sup>4</sup> The yield of the reaction (88 %) was determined by NMR with mesitylene as the internal standard.

Optical purity: 89% ee<sub>s</sub>.

Ee<sub>s</sub> were determined by GC (HP-Chiral β column, 30m × 0.25 mm, oven: 80° C for 1 min, then 1° C/min to 160 °C, 5 min): t<sub>1</sub> = 169.71 min (5.75%) , t<sub>2</sub> = 171.67 min (94.25%).

**3,3'-Dibromo-BINOL catalyzed reaction.** (*R*)-3,3'-dibromo-1,1'-bi-2-naphthol (0.011 g, 0.025 mmol), α,α,α-trifluorotoluene (1.25 mL), toluene (0.25 mL) and 1-formyl-6-methoxy-3,4-dihydronaphthalene (0.048 g, 0.25 mmol) were mixed together under argon and cooled to –35 °C. The allylboronic acid pinacol ester (0.029 g, 0.17 mmol) was added dropwise. The reaction mixture was stirred at – 35 °C for 18 h. The saturated NH<sub>4</sub>Cl aqueous solution (5 mL) was added dropwise to quench the reaction, followed by extraction with dichloromethane (3×5 mL). The combined organic fractions were dried over anhydrous MgSO<sub>4</sub>. Volatiles were removed under reduced pressure.<sup>37</sup> The yield of the reaction (70 %) was determined by NMR with mesitylene as the internal standard.

Optical purity: racemic.

Ee<sub>s</sub> were determined by GC (HP-Chiral β column, 30m × 0.25 mm, oven: 80° C for 1 min, then 1° C/min to 160 °C, 5 min): t<sub>1</sub> = 56.36 min (50%) , t<sub>2</sub> = 57.07 min (50%).

**Ti(IV) mediated reaction.** A mixture of (S)-(+)-1,1'-bi-2-naphthol (0.29 mg, 1.00 mmol), 1 M Ti(O-*i*-Pr)<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub> (290 μL, 1.00 mmol), and oven-dried powdered 4-Å sieves (0.4 g) in dichloromethane (10 mL) was heated at reflux for 1 h. The reaction mixture was then cooled to room temperature and 1-formyl-6-methoxy-3,4-dihydronaphthalene (0.188 g, 1.00 mmol) was added. After being stirred for 10 min, the contents were cooled to -78 °C and allyltri-*n*-butylstannane (0.369 g, 1.11 mmol) was added. The reaction was stirred for 10 min and then placed into a freezer (a -20 °C) for 168 h. Then saturated aqueous solution of NaHCO<sub>3</sub> (2 mL) was added dropwise to quench the reaction, followed by extraction with dichloromethane (3×10 mL). The collected organic fractions were washed with 5% HCl (50 mL). Volatiles were removed under reduced pressure.<sup>19</sup> Column chromatography of the residue (CH<sub>2</sub>Cl<sub>2</sub>) on silica gel yielded 0.042 g (35 %) of the title compound yielded 0.060 g (26 %) as a colorless oil.

Optical purity: 94.8 % ee<sub>s</sub>.

Ee<sub>s</sub> were determined by GC (HP-Chiral β column, 30m × 0.25 mm, oven: 80° C for 1 min, then 1° C/min to 160 °C, 5 min): t<sub>1</sub> = 55.6 min (97.4%) , t<sub>2</sub> = 56.3 min (2.6%).

**(*R,R*)-8a catalyzed reaction in THF.** To a solution of (*R,R*)-3-phenyl-3'-(tetrahydrofuran-2-yl)-5,5',6,6',7,7',8,8'-octahydro-1,1'-biisoquinoline 2,2'-dioxide (0.021 g, 0.005 mmol) in THF (2 mL), 1-formyl-6-methoxy-3,4-dihydronaphthalene (0.018 g, 0.1 mmol), diisopropylethylamine (17 μL, 0.1 mmol) were added under argon atmosphere, and cooled to -40 °C. Allyltrichlorosilane (20 μL, 0.14 mmol) was added. The reaction mixture was stirred for 18 h at -40 °C. Saturated NaHCO<sub>3</sub> (2 mL) was added dropwise to quench the reaction, followed by extraction with dichloromethane (3×10 mL). The combined organic fractions were washed with 5%

HCl (50 mL). Volatiles were removed under reduced pressure.<sup>13</sup> The yield of the reaction (above 90 %) was determined by NMR with mesitylene as the internal standard.

Optical purity: 68% ee<sub>s</sub>.

Ee<sub>s</sub> were determined by GC (HP-Chiral β column, 30m × 0.25 mm, oven: 80° C for 1 min, then 1° C/min to 160 °C, 5 min): t<sub>1</sub> = 167.179 min (16%) , t<sub>2</sub> = 169.086 min (84%).

**(*R,R*)-8a catalyzed reaction in DCM.** To a solution of (*R,R*)-3-phenyl-3'-(tetrahydrofuran-2-yl)-5,5',6,6',7,7',8,8'-octahydro-1,1'-biisoquinoline 2,2'-dioxide (0.089 g, 0.02 mmol) in dichloromethane (2 mL), 1-formyl-6-methoxy-3,4-dihydronaphthalene (0.038 g, 0.2 mmol), diisopropylethylamine (34 μL, 0.2 mmol) were added under argon atmosphere, and cooled to -40 °C. Allyltrichlorosilane (40 μL, 0.28 mmol) was added. The reaction mixture was stirred for 18 h at -40 °C. Saturated NaHCO<sub>3</sub> (2 mL) was added dropwise to quench the reaction, followed by extraction with dichloromethane (3×10 mL). The combined organic fractions were washed with 5% HCl (50 mL). Volatiles were removed under reduced pressure.<sup>13</sup> The yield of the reaction (55 %) was determined by NMR with mesitylene as the internal standard.

Optical purity: 66% ee<sub>s</sub>.

Ee<sub>s</sub> were determined by GC (HP-Chiral β column, 30m × 0.25 mm, oven: 80° C for 1 min, then 1° C/min to 160 °C, 5 min): t<sub>1</sub> = 168.75 min (83%) , t<sub>2</sub> = 170.79 min (17%).

**(*R,S*)-8a catalyzed reaction.** To a solution of (*R,S*)-3-phenyl-3'-(tetrahydrofuran-2-yl)-5,5',6,6',7,7',8,8'-octahydro-1,1'-biisoquinoline 2,2'-dioxide (0.021 g, 0.005 mmol)

in THF (2 mL), 1-formyl-6-methoxy-3,4-dihydronaphthalene (0.018 g, 0.1 mmol), diisopropylethylamine (17  $\mu$ L, 0.1 mmol) were added under argon atmosphere, and cooled to -40 °C. Allyltrichlorosilane (20  $\mu$ L, 0.14 mmol) was added. The reaction mixture was stirred for 18 h at -40 °C. Saturated NaHCO<sub>3</sub> (2 mL) was added dropwise to quench the reaction, followed by extraction with dichloromethane (3 $\times$ 10 mL). The combined organic fractions were washed with 5% HCl (50 mL). Volatiles were removed under reduced pressure.<sup>13</sup> The yield of the reaction (above 90 %) was determined by NMR with mesitylene as the internal standard.

Optical purity: 60% ee<sub>s</sub>.

Ee<sub>s</sub> were determined by GC (HP-Chiral  $\beta$  column, 30m  $\times$  0.25 mm, oven: 80° C for 1 min, then 1° C/min to 160 °C, 5 min): t<sub>1</sub> = 167.18 min (80%) , t<sub>2</sub> = 169.09 min (20%).

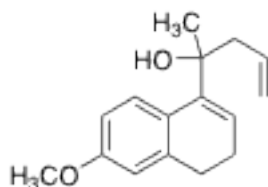
**(*R,S,R*)-8a catalyzed reaction.** To a solution of (*R,S,R*)-3-phenyl-3'-(tetrahydrofuran-2-yl)-5,5',6,6',7,7',8,8'-octahydro-1,1'-biisoquinoline 2,2'-dioxide (0.020 g, 0.005 mmol) in THF (2 mL), 1-formyl-6-methoxy-3,4-dihydronaphthalene (0.018 g, 0.1 mmol), diisopropylethylamine (17  $\mu$ L, 0.1 mmol) were added under argon atmosphere, and cooled to -40 °C. Allyltrichlorosilane (20  $\mu$ L, 0.14 mmol) was added. The reaction mixture was stirred for 18 h at -40 °C. Saturated NaHCO<sub>3</sub> (2 mL) was added dropwise to quench the reaction, followed by extraction with dichloromethane (3 $\times$ 10 mL). The combined organic fractions were washed with 5% HCl (50 mL). Volatiles were removed under reduced pressure.<sup>13</sup> The yield of the reaction (68 %) was determined by NMR with mesitylene as the internal standard.

Optical purity: 22% ee<sub>s</sub>.

Ee<sub>s</sub> were determined by GC (HP-Chiral  $\beta$  column, 30m  $\times$  0.25 mm, oven: 80° C for 1 min, then 1° C/min to 160 °C, 5 min): t<sub>1</sub> = 167.18 min (61%) , t<sub>2</sub> = 169.09 min (39%).

## 5.2.2. Allylations of $\alpha,\beta$ -unsaturated ketone 39b

### 2-(6-Methoxy-3,4-dihydronaphthalen-1-yl)pent-4-en-2-ol (44b).



**Racemic synthesis.** 1-(6-methoxy-3,4-dihydronaphthalen-1-yl)ethanone (0.050 g, 0.25 mmol) was dissolved in distilled THF (2 ml) and left to cool under argon in dry ice. Allylmagnesium bromide (0.4 mL, 0.4 mmol) was added, and the reaction mixture was left for 5h. Water was added dropwise to quench the reaction mixture, followed by extraction with dichloromethane (3×5 mL). The organic fractions were washed with 5% HCl (1 mL). Volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel in dichloromethane, to yield 0.029 g (48 %) of the title compound as a colorless oil.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.65-7.75 (m, 1H), 6.7-6.8 (m, 2H), 6.1-6.2 (m, 1H), 5.6-5.8 (m, 1H), 5.0-5.1 (m, 2H), 3.8 (m, 3H), 2.6-2.8 (m, 2H), 2.5-2.6 (m, 2H), 2.4 (m, 3H), 2.3-2.4 (m, 2H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  23.12 ( $\text{CH}_2$ ), 28.53 ( $\text{ArCH}_2$ ), 29.52 ( $\text{CH}_3$ ), 45.83 ( $\text{CH}_2$ ), 55.16 ( $\text{OCH}_3$ ), 74.34 ( $\text{COH}$ ), 110.50 (Ar), 113.71 (Ar), 118.63 ( $\text{C}=\text{CH}$ ), 123.37 (Ar), 126.37 ( $\text{C}=\text{CH}$ ), 127.18 (Ar), 134.16 (Ar), 140.03 ( $\text{C}=\text{CH}$ ), 141.11 ( $\text{C}=\text{CH}$ ), 157.86 (Ar).

IR (KBr)  $\nu$  3198, 3075, 3060, 3004, 2995, 2977, 2935, 2906, 2824, 1640, 1598, 1568, 1500, 1461, 1434, 1374, 1356, 1299, 1248, 1123, 1099, 1045, 916, 836.

HRMS (EI+) calcd. for  $\text{C}_{16}\text{H}_{20}\text{O}_2\text{Na}$  267.13563, found 267.13555.

$R_f(\text{CH}_2\text{Cl}_2) = 0.3$

Optical purity: racemic

**Ag(I)-catalyzed reaction.** AgOTf (0.0016 g, 0.0125 mmol), (*S*)-DIFLUORPHOS (0.008 g, 0.0125 mmol) and MeOH (0.75 ml) were mixed together and dried under vacuum (5 mmHg) for 1 h. The mixture was then cooled to -78 °C. MeOH (10 µl) and THF (1.5 ml) were added and stirred for 10 min. Following, allyltrimethoxysilane (84,5 µl, 0.5 mmol) and 1-(6-methoxy-3,4-dihydronaphthalen-1-yl)ethanone (0.050 g, 0.25 mmol) were added successively and the reaction mixture was left to stir at -78°C for 18 h. The reaction mixture was then quenched by vacuum column chromatography in dichloromethane.<sup>38</sup> The yield of the reaction (10 %) was determined by NMR with mesitylene as the internal standard.

Optical purity: 88 % ee<sub>s</sub>.

Ee<sub>s</sub> were determined by GC (HP-Chiral β column, 30m × 0.25 mm, oven: 80° C for 1 min, then 1° C/min to 160 °C, 5 min): t<sub>1</sub> = 132 min (6%), t<sub>2</sub> = 133.12 min (94%).

**Ag(I) catalyzed reaction.** AgOTf (0.0048 g, 0.0375 mmol), (*S*)-DIFLUORPHOS (0.026 g, 0.0375 mmol) and MeOH (0.75 ml) were mixed together and dried under vacuum (5 mmHg) for 1 h. The mixture was then cooled to -78 °C. MeOH (10 µl) and THF (1.5 ml) were added and stirred for 10 min. Following, allyltrimethoxysilane (84,5 µl, 0.5 mmol) and 1-(6-methoxy-3,4-dihydronaphthalen-1-yl)ethanone (0.050 g, 0.25 mmol) were added successively and the reaction mixture was left to stir at -78°C for 18 h. The reaction mixture was then quenched by vacuum column chromatography in dichloromethane.<sup>38</sup> The yield of the reaction (90 %) was determined by NMR with mesitylene as the internal standard.

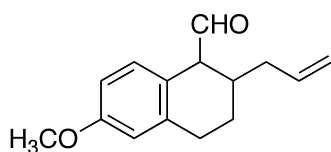
Optical purity: 92% ee<sub>s</sub>.

Ee<sub>s</sub> were determined by GC (HP-Chiral β column, 30m × 0.25 mm, oven: 80° C for 1 min, then 1° C/min to 160 °C, 5 min): t<sub>1</sub> = 131 min (4%) , t<sub>2</sub> = 132.83 min (96%).



### 5.3. Other reactions

#### 2-Allyl-6-methoxy-1,2,3,4-tetrahydronaphthalene-1-carbaldehyde (45).



To a solution of 1-(6-methoxy-3,4-dihydronaphthalen-1-yl)but-3-en-1-ol (0.5 g, 2.2 mmol), 18-crown-6 in THF, potassium hydride (0.176 g, 4.4 mmol) was added under argon atmosphere. The reaction mixture was placed into a microwave reactor for 20 min (180 °C). Then the reaction mixture was extracted with dichloromethane (3×30 mL). The organic fractions were washed with 5% HCl (50 mL). Volatiles were removed under reduced pressure.<sup>42</sup> The residue was purified on silica gel column chromatography in dichloromethane to yield 0.4 g (80 %) of the title compound as a colorless oil.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.5-9.6 (m, 1H), 6.9-7.0 (m, 1H), 6.7-6.8 (m, 2H), 5.8-6.0 (m, 1H), 5.0-5.2 (m, 2H), 3.7-3.8 (m, 3H), 3.3-3.4 (m, 1H), 2.7-2.9 (m, 2H), 2.0-2.2 (m, 2H), 1.9-2.0 (m, 1H), 1.5-1.7 (m, 2H).

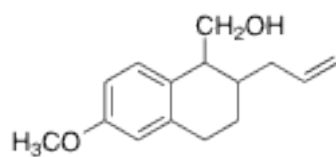
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 25.29 (CH<sub>2</sub>), 27.55 (ArCH<sub>2</sub>), 32.87 (CH), 36.43 (CH<sub>2</sub>), 55.17 (OCH<sub>3</sub>), 56.46 (CH), 112.57 (Ar), 114.36 (Ar), 117.18 (C=CH), 121.96 (Ar), 130.82 (C=CH), 135.89 (Ar), 138.97 (Ar), 158.69 (Ar), 202.03 (CHO).

IR (KBr) ν 3075, 2998, 2992, 2854, 2833, 2705, 1718, 1643, 1607, 1577, 1506, 1461, 1455, 1434, 1257, 1242, 1039.

HRMS (EI+) calcd. for C<sub>15</sub>H<sub>19</sub>O<sub>2</sub> 231.1385, found 231.1388.

R<sub>f</sub> (CH<sub>2</sub>Cl<sub>2</sub>) = 0.5.

**(2-Allyl-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (46).**



2-Allyl-6-methoxy-1,2,3,4-tetrahydronaphthalene-1-

carbaldehyde (0.020 g, 0.106 mmol) was dissolved in ethanol (2 ml). NaBH<sub>4</sub> (0.038 g, 0.106 mmol) was added, and the reaction mixture was left at room temperature for 2 hours. The solution of 5% NaHCO<sub>3</sub> (5 mL) was added dropwise to quench the reaction, followed by extraction with dichloromethane (3×5 mL). The combined organic fractions were dried over anhydrous MgSO<sub>4</sub>. Volatiles were removed under reduced pressure to yield 0.024 g (97 %) of the title compound as a colorless oil.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 7.0-7.1 (m, 1H), 6.6-6.7 (m, 2H), 5.8-6.0 (m, 1H), 5.0-5.2 (m, 2H), 3.7-3.8 (m, 3H), 3.5-3.7 (m, 2H), 2.6-2.8 (m, 2H), 2.0-2.2 (m, 2H), 1.8-2.0 (m, 2H), 1.5-1.6 (m, 1H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 23.86 (CH<sub>2</sub>), 26.46 (ArCH<sub>2</sub>), 33.35 (CH), 37.87 (CH<sub>2</sub>), 44.89 (CH<sub>2</sub>OH), 55.17 (OCH<sub>3</sub>), 67.19 (CH), 112.22 (Ar), 113.64 (Ar), 116.17 (C=CH), 127.96 (Ar), 130.66 (C=CH), 137.25 (Ar), 139.07 (Ar), 157.83 (Ar).

IR (KBr) ν 3383, 3072, 3055, 2998, 2923, 2875, 2833, 1640, 1613, 1574, 1556, 1538, 1506, 1470, 1449, 1431, 1335, 1314, 1254, 1159, 1042, 911.

HRMS (EI<sup>+</sup>) calcd. for C<sub>15</sub>H<sub>20</sub>O<sub>2</sub> 232.1463, found 232.1455.

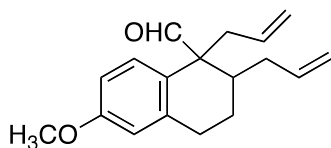
R<sub>f</sub> (CH<sub>2</sub>Cl<sub>2</sub>) = 0.45.

**Mosher's ester (47) preparation.** To a solution of DMAP (0.024 g, 0.2 mmol) and (2-allyl-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (0.009 g, 0.04 mmol) in dichloromethane (2 ml) was added under argon atmosphere (*R*)-(-)- $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetylchloride (0.010 g, 0.02 mmol). The reaction mixture was left stirring overnight at room temperature. The solution of 5% NaHCO<sub>3</sub> (5 mL) was

added dropwise to quench the reaction, followed by extraction with dichloromethane (3×5 mL). The combined organic fractions were dried over anhydrous MgSO<sub>4</sub>. Volatiles were removed under reduced pressure. The obtained diastereometric Mosher's esters were used to determine enantiomeric excess without further purification.

Optical purity: 20% ee<sub>s</sub>.

### 1,2-Diallyl-6-methoxy-1,2,3,4-tetrahydronaphthalene-1-carbaldehyde (48).



A solution of 2-allyl-6-methoxy-1,2,3,4-tetrahydronaphthalene-1-carbaldehyde (0.030 g, 0.13 mmol) in DMF was cooled to 0 °C under argon atmosphere. Allylbromide (0.028 g, 0.23 mmol) was added to reaction mixture. Potassium *tert*-butoxide (0.017 g, 0.16 mmol) was divided into 4 fractions and added to reaction mixture in 5 minutes intervals. Reaction was then left stirring at 0 °C for 1 hour under argon atmosphere. Water was added to quench the reaction, followed by extraction with dichloromethane (3×30 mL). The organic fractions were washed with 5% HCl (50 mL). Volatiles were removed under reduced pressure.<sup>43</sup> The residue was purified on silica gel column chromatography in dichloromethane/hexane (1/1) to yield 0.010 g (31 %) of the title compound as a colorless oil.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.6-9.7 (m, 1H), 7.0 (m, 1H), 6.7-6.8 (m, 2H), 5.7-5.8 (m, 1H), 5.2-5.4 (m, 1H), 4.9-5.2 (m, 4H), 3.8 (m, 3H), 1.5-1.7 (m, 2H), 1.2-1.4 (m, 2H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 24.78 (CH<sub>2</sub>), 30.07 (ArCH<sub>2</sub>), 34.66 (CH), 36.93 (CH<sub>2</sub>), 38.38 (CH<sub>2</sub>), 55.13 (OCH<sub>3</sub>), 55.43 (C), 112.86 (Ar), 114.24 (Ar), 116.73 (C=CH),

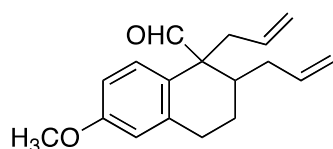
118.30 (C=CH), 125.06 (Ar), 130.02 (C=CH), 134.9 (C=CH), 136.78 (Ar), 141.01 (Ar), 158.43 (Ar), 200.95 (CHO).

IR (KBr)  $\nu$  3075, 3060, 3016, 2998, 2971, 2950, 2932, 2839, 2738, 1858, 1712, 1640, 1607, 1577, 1500, 1464, 1455, 1320, 1242, 1036, 934.

HRMS (EI+) calcd. for C<sub>18</sub>H<sub>23</sub>O<sub>2</sub> 271.1698, found 271.1708.

R<sub>f</sub> (CH<sub>2</sub>Cl<sub>2</sub>) = 0.6.

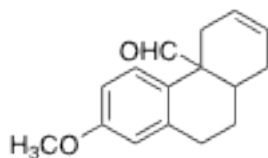
### 1,2-Diallyl-6-methoxy-1,2,3,4-tetrahydronaphthalene-1-carbaldehyde



A solution of 2-allyl-6-methoxy-1,2,3,4-

tetrahydronaphthalene-1-carbaldehyde (0.230 g, 1.0 mmol) in DMF was cooled to 0 °C under argon atmosphere. Allylbromide (0.650 g, 5.0 mmol) was added to reaction mixture. Potassium *tert*-butoxide (0.146 g, 1.3 mmol) was divided into 6 fractions and added to reaction mixture in 5 minutes intervals. Reaction was then left stirring at 0 °C for 90 minutes under argon atmosphere. Water was added to quench the reaction, followed by extraction with dichloromethane (3×30 mL). The organic fractions were washed with 5% HCl (50 mL). Volatiles were removed under reduced pressure.<sup>43</sup> The residue was purified on silica gel column chromatography in dichloromethane/hexane (1/1) to yield 0.230 g (73 %) of the title compound as a colorless oil.

### 7-Methoxy-1,4,4a,9,10,10a-hexahydrophenanthrene-4a-carbaldehyde (49).



1,2-Diallyl-6-methoxy-1,2,3,4-tetrahydronaphthalene-1-

carbaldehyde (0.060 g, 0.22 mmol) was dissolved in dichloromethane under argon

atmosphere. Grubbs II catalyst (0.010 g, 0.11 mmol) was added to reaction mixture. The reaction mixture was stirred for 18 h at room temperature. Volatiles were then removed under reduced pressure.<sup>44</sup> The residue was purified on silica gel column chromatography in ethyl acetate/hexane (1/5) to yield 0.046 g (86 %) of the title compound as a colorless oil.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.6-9.7 (m, 1H), 7.0 (m, 1H), 6.7-6.8 (m, 2H), 5.7-5.8 (m, 2H), 3.8 (m, 3H), 2.9-3.2 (m, 4H), 2.0-2.3 (m, 4H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 25.15 (CH<sub>2</sub>), 29.92 (ArCH<sub>2</sub>), 30.40 (CH), 33.49 (CH<sub>2</sub>), 37.61 (CH<sub>2</sub>), 51.18 (C), 55.16 (OCH<sub>3</sub>), 112.80 (Ar), 114.18 (Ar), 125.79 (Ar), 126.78 (C=CH), 127.07 (C=CH), 128.60 (Ar), 139.49 (Ar), 158.53 (Ar), 200.72 (CHO).

IR (KBr) ν 3389, 3019, 2995, 2929, 2950, 2836, 2723, 1715, 1670, 1604, 1574, 1497, 1467, 1452, 1428, 1317, 1284, 1260, 1239, 1159, 1135, 1039, 665.

HRMS (EI+) calcd. for C<sub>16</sub>H<sub>19</sub>O<sub>2</sub> 243.1385, found 243.1396.

R<sub>f</sub> (1/5 EtOAc/Hex) = 0.5.

## 6. Summary

As previously stated in the objective, the main goal of this work was to develop a new enantioselective synthesis of 6-6-6 condensed ring system from the bicyclic unsaturated aldehyde. In order to accomplish the overall aim several tasks were fulfilled.

a) The allylation of the  $\alpha,\beta$ -unsaturated aldehyde **39a** was tested under broad range of conditions. The Keck's reaction conditions provided the product with the highest enantiomeric excess of 94% but rather low yield of 30 %.

b) The allylation of the  $\alpha,\beta$ -unsaturated ketone **39b** was also evaluated under different conditions. The Ag(I) induced catalysis proved to be the most efficient, providing the product in 90 % yield and with 89 % ee<sub>s</sub>.

c) The potassium hydride mediated oxy-Cope rearrangement was successfully carried out under microwave irradiation giving rise to the product in 80 % yield.

d) The oxy-Cope rearrangement of the chiral alcohol **44a** showed that the optical purity is not fully preserved during the reaction. The enantiomeric excess was partially reduced from 95 % to 20 % ee.

e) Finally, the tricyclic 6-6-6 condensed ring framework **49** was synthesized via potassium *tert*-butoxide induced  $\alpha$ -allylation, followed by Grubbs II catalyzed metathesis. The product was obtained in 62 % overall yield.

## **7. Acknowledgement**

First of all, I would like to thank my supervisor, professor Martin Kotora for the interesting topic of my diploma thesis and for valuable advice and guidance.

I would also like to thank the following people for their help with instrumental analysis: RNDr. Stanislav Hilgard CSc. and Mgr. Martin Popr for measurement and interpretation of IR spectra, and Dr. Irena Valterová for measurements on GC with a chiral stationary phase.

## 8. Abstract

In this work a new route for an enantioselective synthesis of 6–6–6 condensed ring system from a bicyclic unsaturated aldehyde is described. This novel synthesis consisted in allylation of a  $\alpha,\beta$ -unsaturated bicyclic aldehyde followed by the oxy-Cope rearrangement, which afforded a crucial intermediate. Further transformation and Grubbs II catalyzed metathesis provided the 6-6-6 condensed ring scaffold with the angular formyl group.

The enantioselective synthesis was based on Ti(IV)/BINOL mediated allylation of the  $\alpha,\beta$ -unsaturated bicyclic aldehyde, which provided the product with the highest enantiomeric excess of 95%. The following oxy-Cope rearrangement showed a partial loss of the optical purity (down to 20%).

Tato práce popisuje novou enantioselektivní syntézu 6-6-6 kondenzovaného kruhového systému z bicyklického nenasyceného aldehydu. Tato nová syntéza byla založena na allylaci  $\alpha$ ,  $\beta$ -nenasyceného aldehydu a oxy-Cope přesmyku, čímž byl získán klíčový meziprodukt. Další transformace a Grubbs II katalyzovaná metateze vedly k vytvoření 6-6-6 kondenzovaného kruhového systému s angulární formylovou skupinou.

Enantioselektivní syntéza byla založena na allylaci  $\alpha$ ,  $\beta$ -nenasyceného aldehydu zprostředkovanou systémem složeným z Ti(IV)/BINOL, která poskytla produkt s nejvyšším enantiomerním přebytkem 95 % ee. Následný oxy-Copeho přesmyk proběhl však z částečnou ztrátou optické čistoty (až do 20 %).



## 8. References

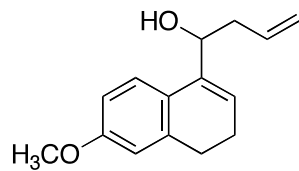
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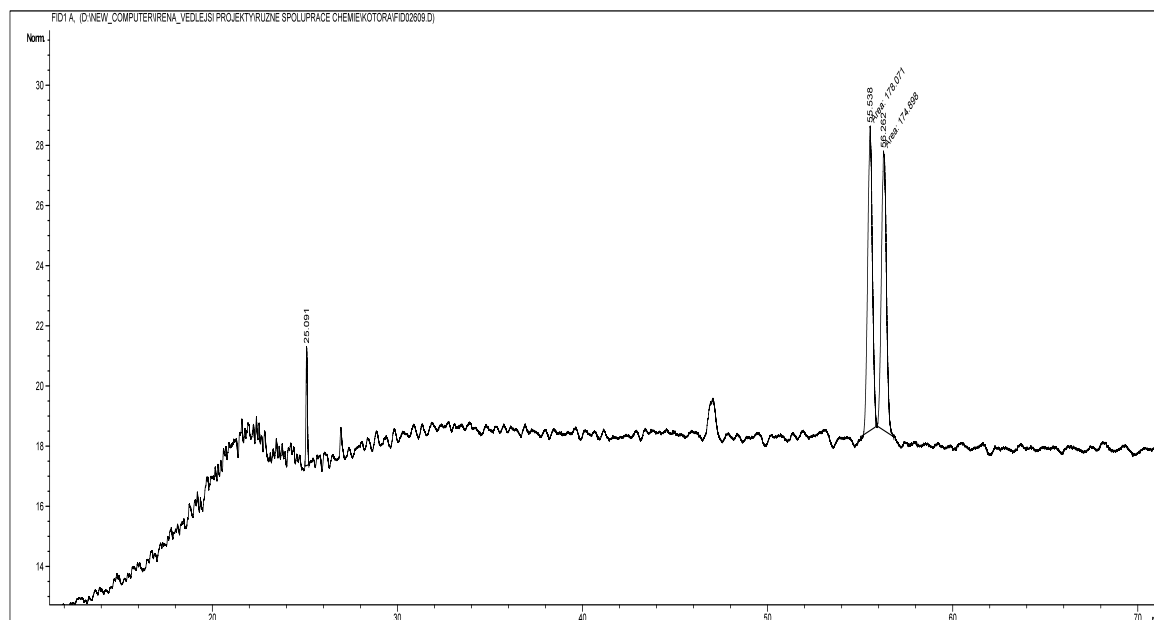
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## Appendix 1

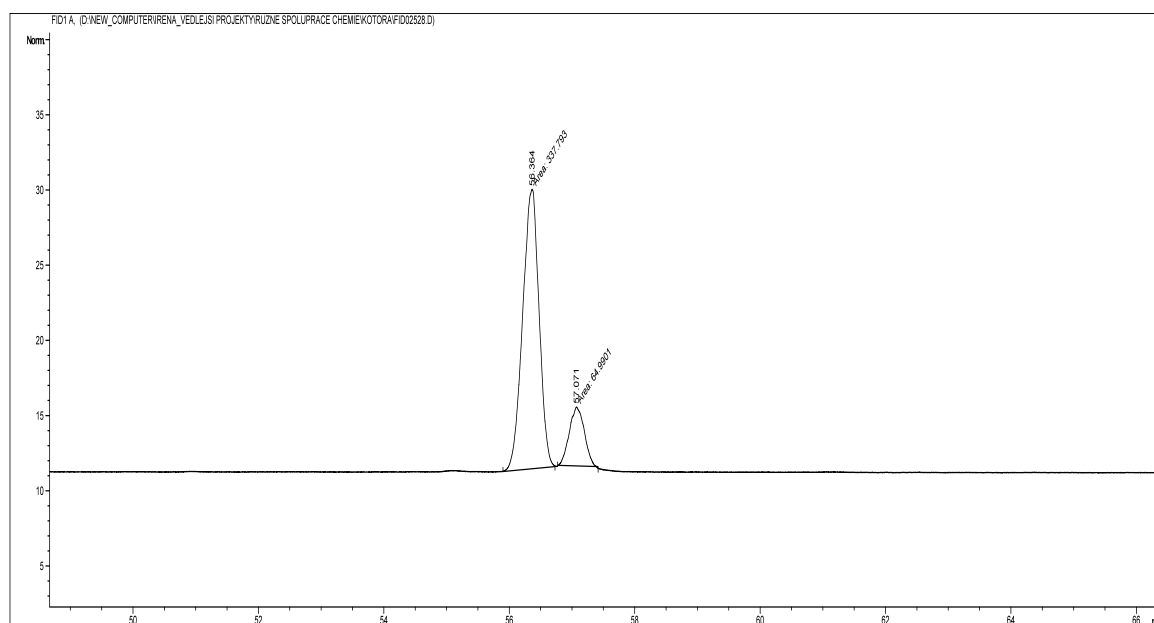
### 1-(6-Methoxy-3,4-dihydronaphthalen-1-yl)but-3-en-1-ol (44a).



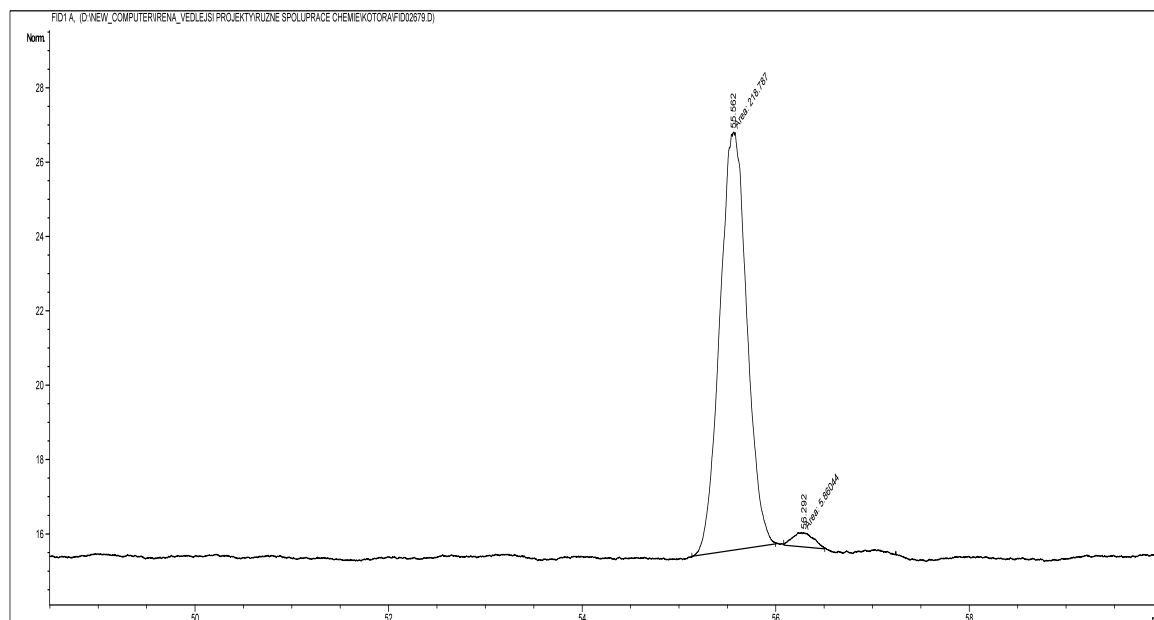
### Racemic allylation of $\alpha,\beta$ -unsaturated aldehyde



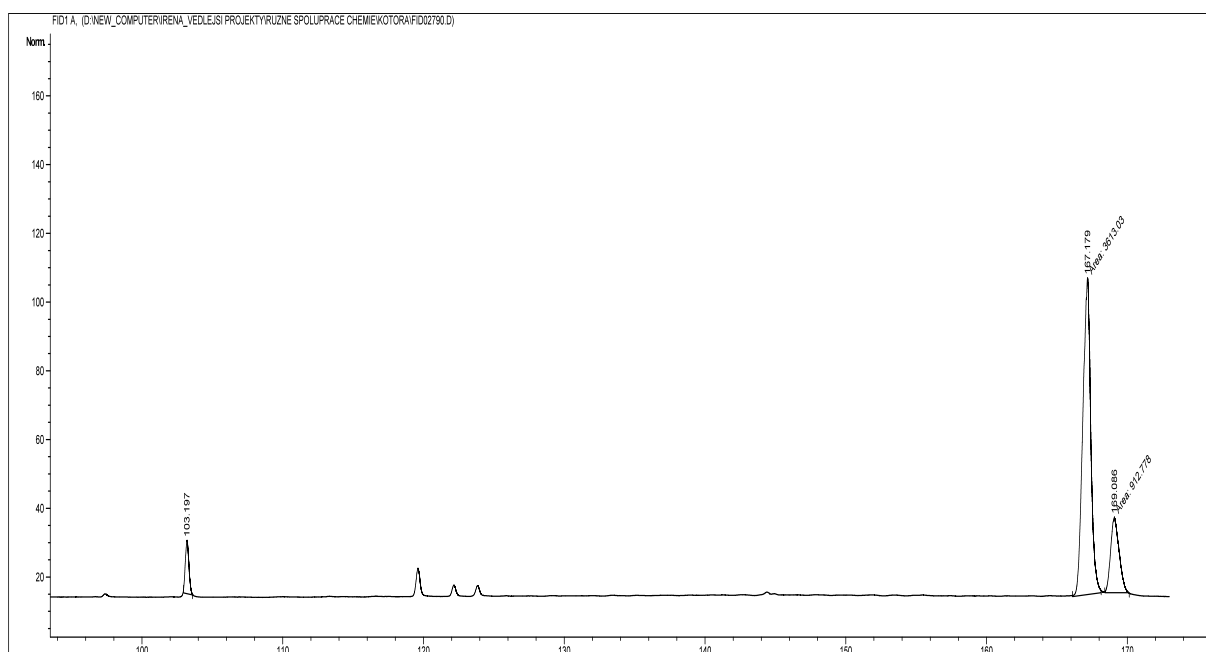
### (S)-TRIP-PA catalyzed allylation of $\alpha,\beta$ -unsaturated aldehyde (68 % ee)



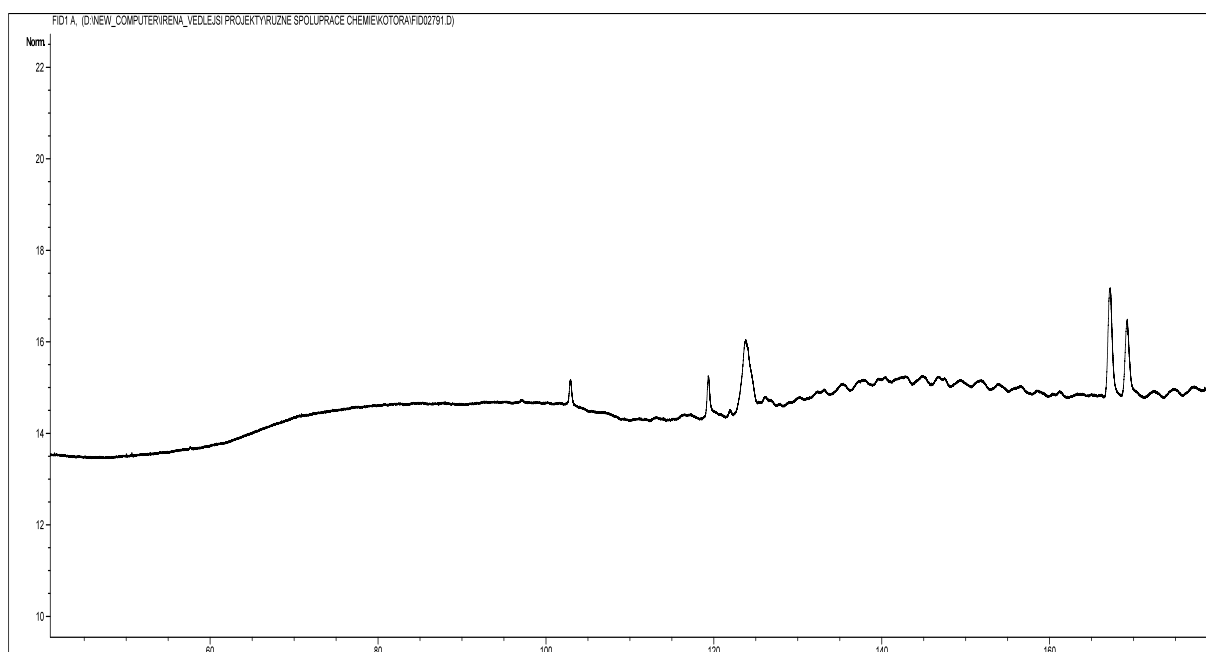
### Ti(IV) mediated allylation of $\alpha,\beta$ -unsaturated aldehyde (95 % ee)



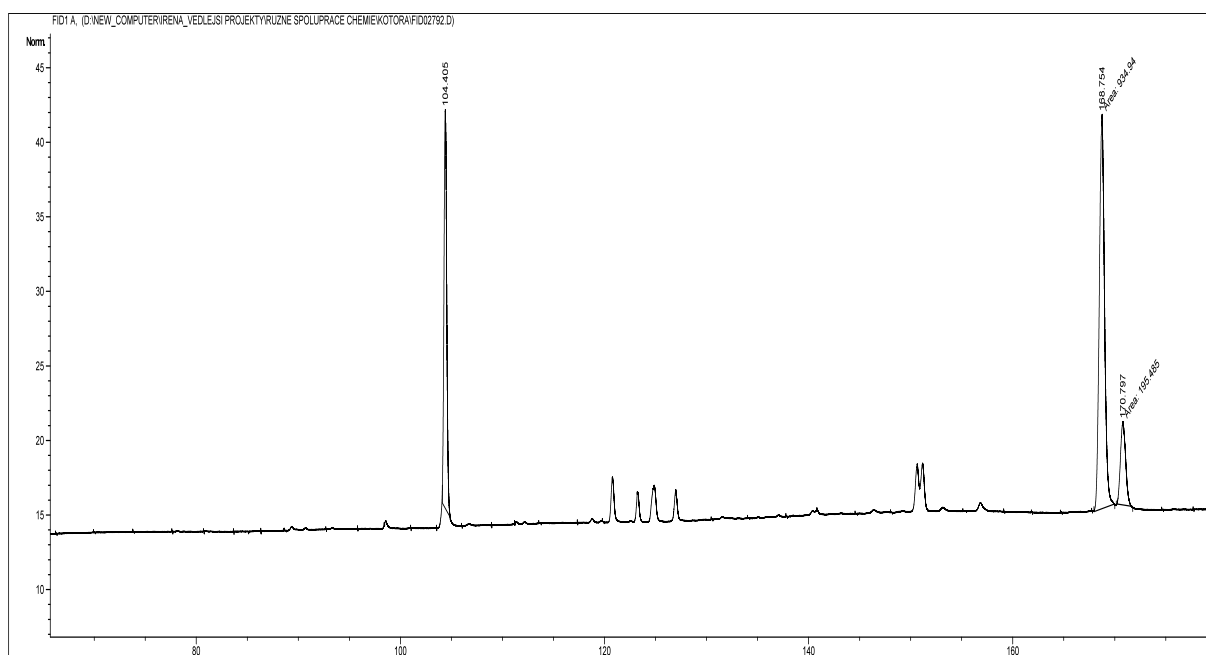
**(*R,S*)-8a catalyzed allylation of  $\alpha,\beta$ -unsaturated aldehyde in THF (60 % ee)**



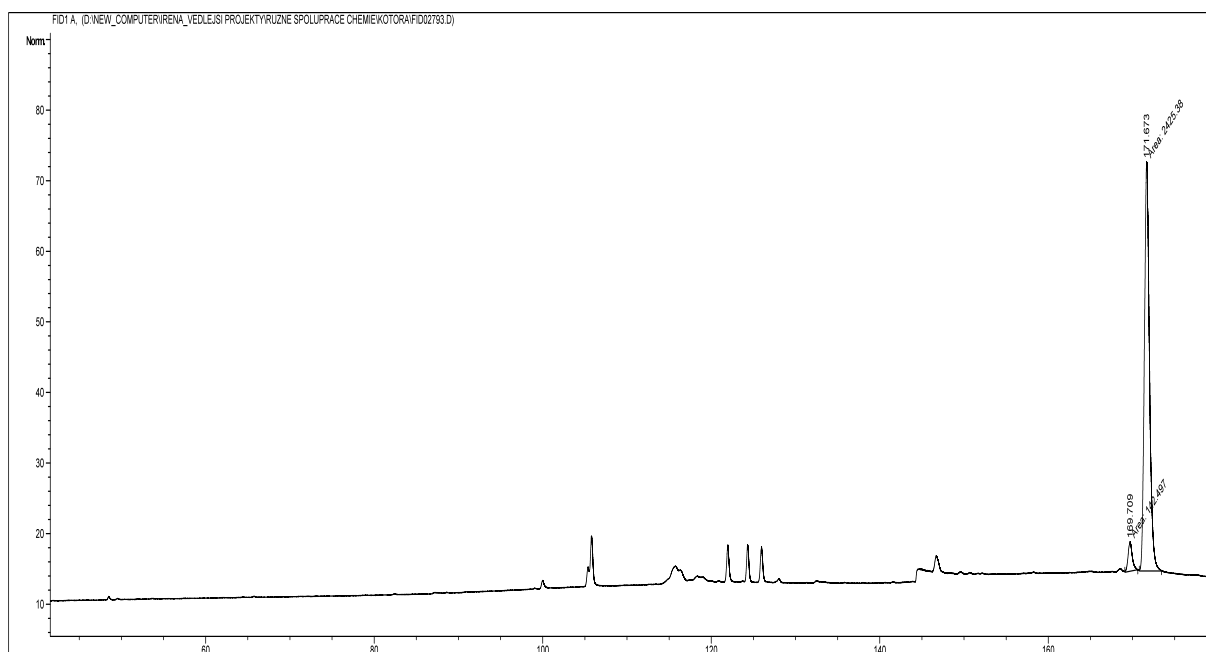
**(*R,S,R*)-8a catalyzed allylation of  $\alpha,\beta$ -unsaturated aldehyde in THF (22 % ee)**



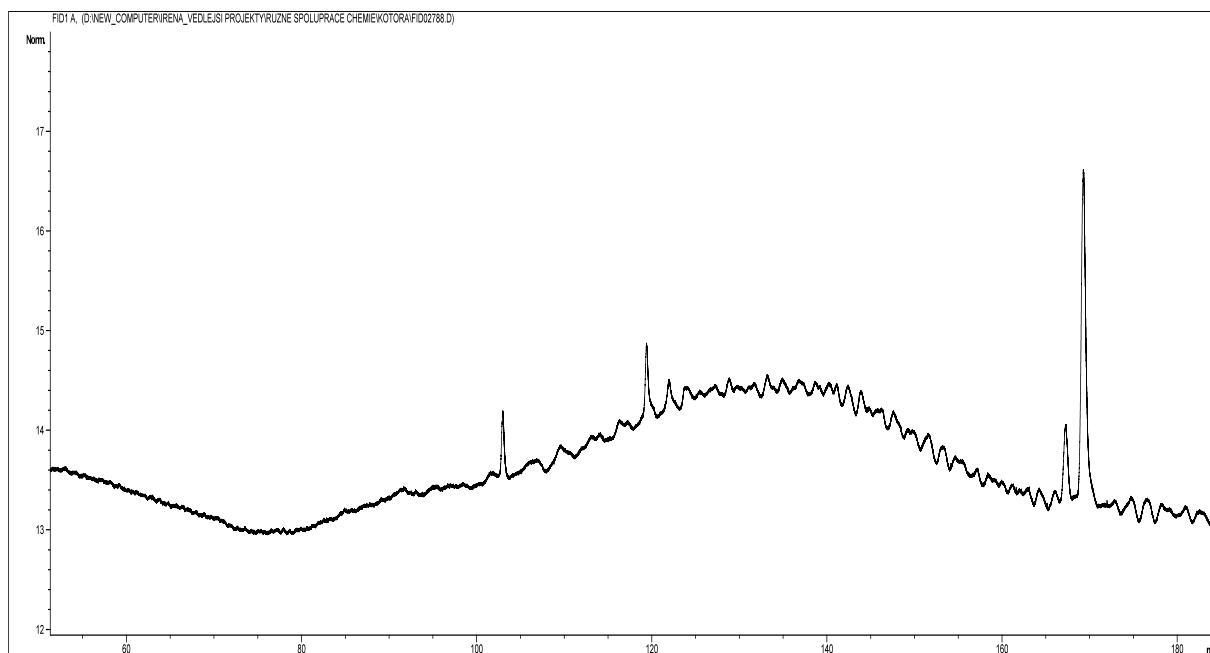
**(R,R)-8a catalyzed allylation of  $\alpha,\beta$ -unsaturated aldehyde in DCM (66 % ee)**



**Ag(I)/BINAP catalyzed allylation of  $\alpha,\beta$ -unsaturated aldehyde (89 % ee)**

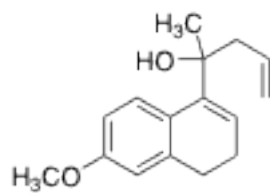


**(*R,R*)-8a catalyzed allylation of  $\alpha,\beta$ -unsaturated aldehyde in THF (68 % ee)**

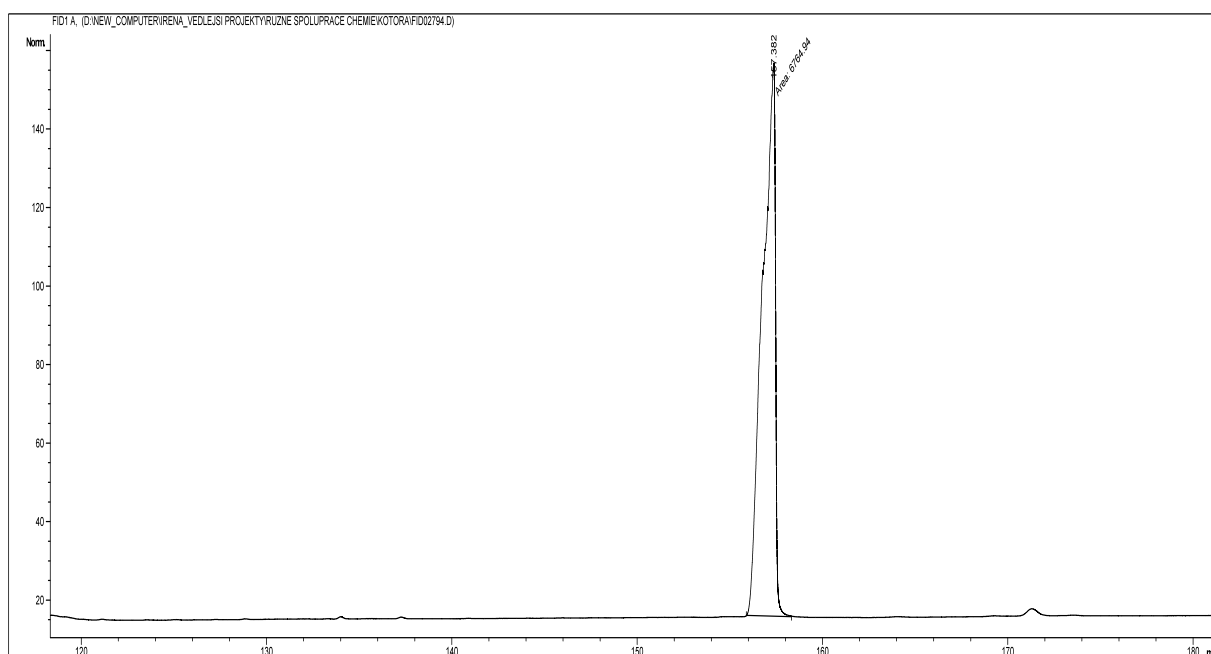




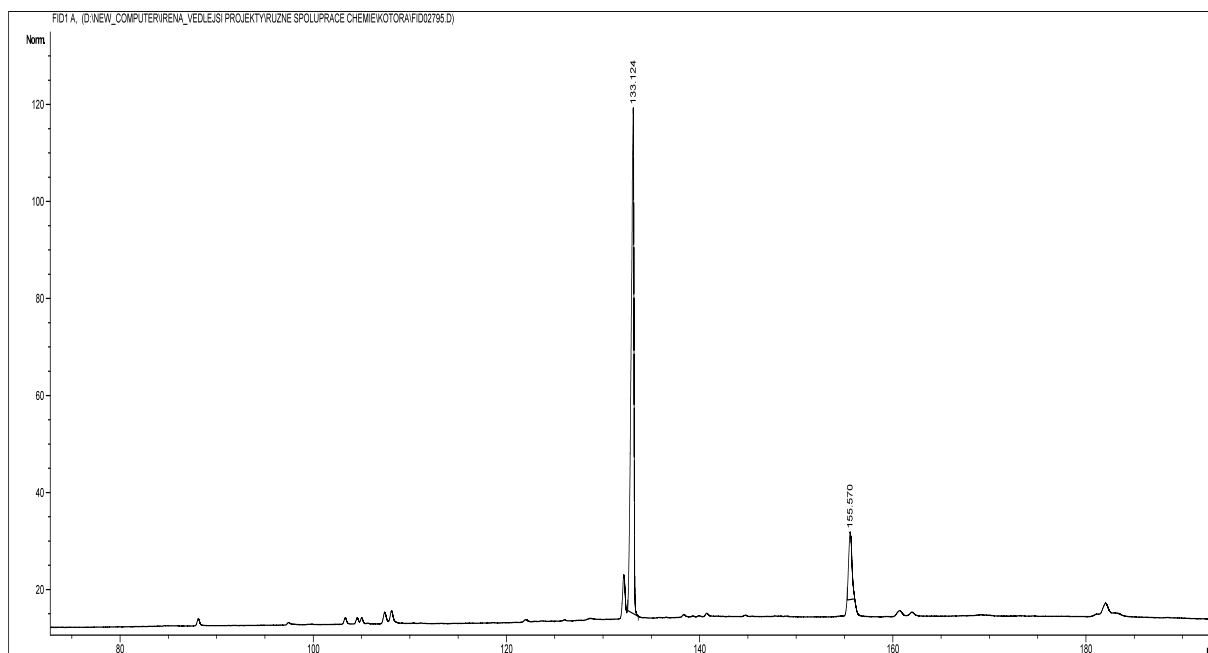
## 2-(6-Methoxy-3,4-dihydronaphthalen-1-yl)pent-4-en-2-ol (44b).



## Racemic allylation of $\alpha,\beta$ -unsaturated ketone



**Ag(I)-catalyzed reaction (5%) allylation of  $\alpha,\beta$ -unsaturated ketone (88 % ee)**



**Ag(I)-catalyzed reaction (15%) allylation of  $\alpha,\beta$ -unsaturated ketone (92 % ee)**

