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# DNA-based catalytic asymmetric allylic substitution

Synthesis of a ligand for DNA-based catalysis able to coordinate to iridium(I).

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## **Abstract**

In this project a ligand was synthesized, that is suitable to interact with DNA and at the same time is able to coordinate iridium(I). The ligand was obtained by a parallel synthesis of a diene functionality, that is able to coordinate iridium(I) and an acridine moiety, which is known as an intercalator. Both parts were coupled in the last step.

Many difficulties were experienced during the synthesis. Diene containing moieties are found to be unstable under strong acidic environments, high temperatures and light. Acridine containing functionalities can degrade to acridone by means of a hydrolysis reaction. This can occur both in the presence of acid and base. The ligand was not obtained pure, but it is believed that the impurity, mainly acridone, can be removed using column chromatography.

The catalyst system is expected to be able to catalyze allylic substitutions, where the chirality of DNA is transferred to the products of the reaction, resulting in an enantiomeric excess.

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# 1. Introduction

## 1.1 DNA-based catalysis

The characteristic right-handed double helix structure of DNA is one of the most well known examples of chirality in nature. It is therefore not surprising that the scope of hybrid catalysis, in which catalytically active transition metals are bound to biopolymer scaffolds, is extended to DNA-based asymmetric catalysis. The main concept of DNA-based asymmetric catalysis implies the use of the double helix of DNA to create a chiral microenvironment around a transition metal. When these are brought in close proximity with the DNA, the chirality of the double helix could be transferred to the product of the reaction.<sup>[1]</sup>

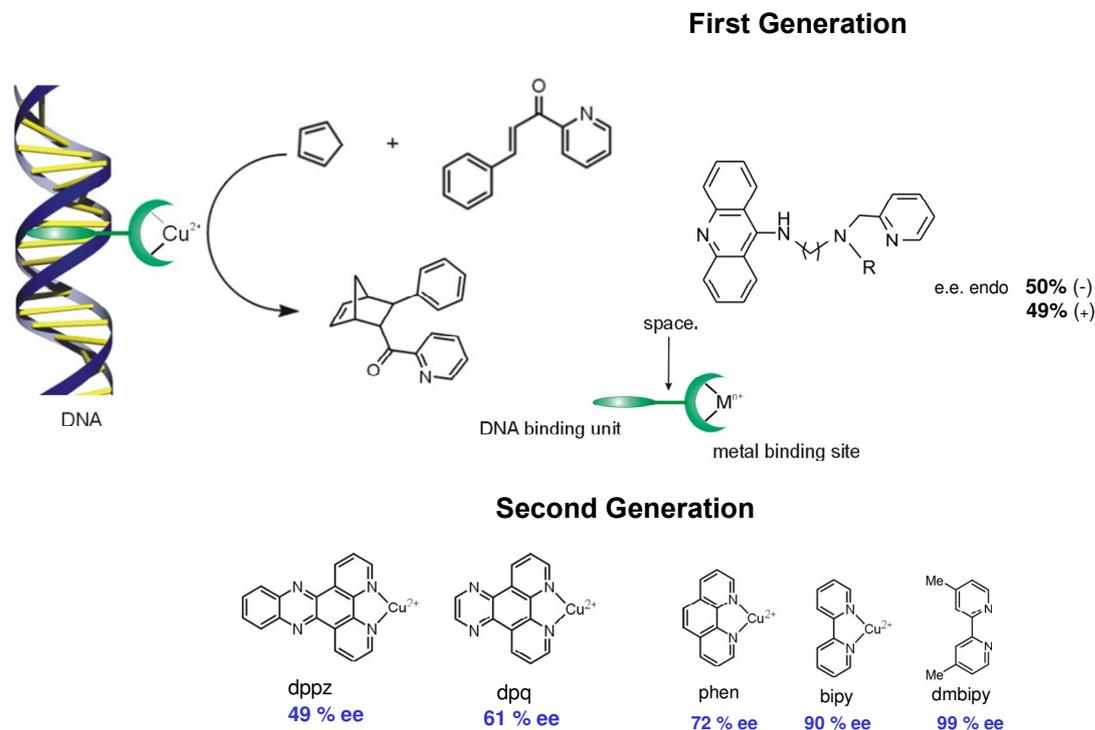
Prochiral substrates can be turned into chiral products, using the chiral information of DNA preferentially directing the reaction towards one enantiomer, resulting in an enantiomeric excess.

The biomolecular features of the catalytic system allow reactions to take place in water. Water as a solvent has several advantages over organic solvents. It is not only cheap and readily available, but also non-toxic and incombustible, which makes it a safe and easily manageable solvent.<sup>[2]</sup>

In 2005 Roelfes and Feringa published the first example of enantioselective DNA-based catalysis, where a Lewis acidic Cu(II) complex was brought in close proximity with DNA by using an intercalating ligand. The first generation of copper complexes was based on ligands containing an acridine moiety, which is able to stack between the base pairs of DNA. (Fig. 1) This acridine was attached to a copper binding moiety via a linker. With this design, enantioselectivities of up to 50% were obtained.<sup>[1]</sup>

These enantioselectivities were increased drastically using bipyridine-type ligands. In 2007 Boersma et al. obtained 99% ee using a copper complex coordinated to 4,4'-dimethyl-2,2'-bipyridine as a catalyst in a Diels Alder cycloaddition reaction between cyclopentadiene and azachalcone.<sup>[3]</sup> (Fig. 1)

The scope and versatility of DNA-based catalysis has been expanded by applying it to other C-C bond forming reactions. Up to 99% ee was reached in Michael reactions between dimethyl malonate and  $\alpha,\beta$ -unsaturated 2-acylimidazoles, using the same dmbpy-based catalyst<sup>[4]</sup> Also Friedel Crafts alkylations have been successfully catalyzed by Cu-dmbpy/DNA. Enantioselectivities of up to 93% were obtained in the reaction of  $\alpha,\beta$ -unsaturated 2-acyl imidazoles with heteroaromatic  $\pi$  nucleophiles.<sup>[5]</sup> Furthermore, enantiomeric excess of up to 74% in fluorination reactions have been obtained in a reaction between  $\beta$ -keto esters and Selectofluor® (a source of fluor) in the presence of Cu-dmbpy/DNA.<sup>[6]</sup> In 2008, the concept of DNA-based catalysis was also applied in a kinetic resolution. In reactions between 2-pyridyloxiranes and water the epoxides were recovered with ee's of up to 63%.<sup>[7]</sup>



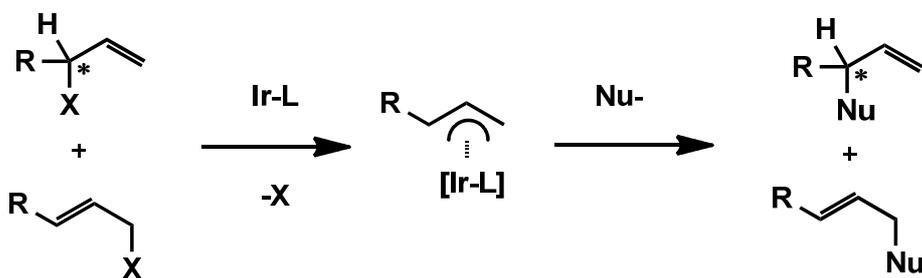
**Figure 1; Cu-L(NO<sub>3</sub>)<sub>2</sub>/DNA Catalyzed Diels Alder Cycloaddition, with different intercalating ligands.**

These systems all rely on Lewis acid catalysis by Cu<sup>2+</sup> ions. In order to make DNA-based catalysis more versatile, it would be of great value to apply it to reactions that are catalyzed by other transition metals.

A first approach to this was published in 2009, when Jäschke and coworkers<sup>[8]</sup> obtained up to 27% ee using a DNA-based system (see section 1.3). This was consisting of the transition metal iridium(I) coordinated to a linker attached to DNA via a covalent bond. These results make iridium(I) an excellent candidate for further investigations applying intercalating ligands.

## 1.2 Asymmetric allylic substitution.

Asymmetric allylic substitution reactions are widely used to create useful chiral building blocks. Both linear and branched allylic substrates can be used for this reaction (Scheme 1). Since the reaction proceeds via an intermediate in which the double bond is delocalized, the nucleophile can attack at two positions of the molecule, resulting in either the branched or the linear allylic product. When an iridium(I) complex is used as a catalyst in this reaction, formation of the branched product is favored over the linear one.<sup>[9]</sup>



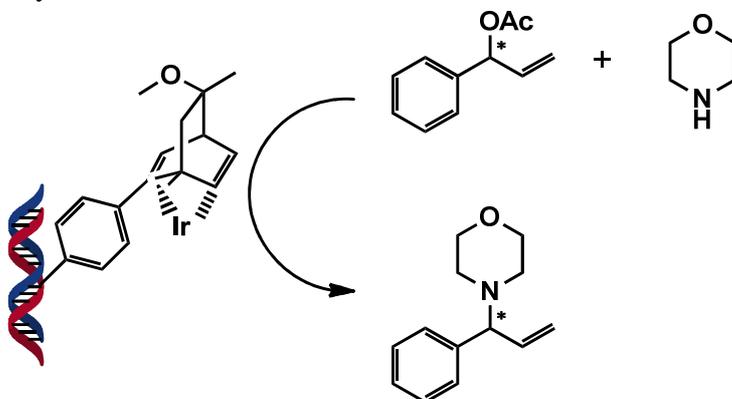
**Scheme 1; Schematic view of iridium-catalyzed asymmetric allylic substitution**

The first iridium-catalyzed asymmetric allylic substitution was reported in 1997 by Helmchen et al.<sup>[10]</sup> Allylic acetates were alkylated with dimethyl malonate in the presence of a catalytic amount of an iridium-complex, resulting in an enantiomeric excess of up to 95%.

In this case a carbon-based nucleophile was used, but allylic substitutions can also be carried out using nitrogen- or oxygen-based nucleophiles.<sup>[9]</sup> This makes asymmetric allylic substitutions extremely valuable and widely applicable in the field of synthetic chemistry.

### 1.3 DNA-based asymmetric allylic substitution.

In 2009, Jäschke et al.<sup>[8]</sup> showed a change in enantioselectivity, when an asymmetric allylic substitution reaction was carried out in both absence and presence of DNA.



**Figure 2; DNA-based allylic amination of allyl phenyl acetate**

The DNA-based catalyst was based on a chiral iridium(I) complex covalently attached to DNA. The allylic amination of phenyl allyl acetate was carried out in the presence of this catalyst. Later a complementary strand was added and the results were compared.

In absence of the complementary strand, an enantiomeric excess of 23% was observed, which changed to -27% in presence of a complementary strand. It is not clear whether the chirality of DNA is actually transferred from the double strand to the products. It is also

possible that this enantioselectivity is originating from the chiral ligand. The change in enantiopreference at the other hand, can only be due to the presence of DNA.

#### 1.4 Goals and Motivation

The goal of this project is to synthesize a ligand that is suitable to interact with DNA and in the mean time carries a diene functionality able to coordinate iridium(I). Intercalation takes place by self-assembly. This approach enables, in contrast to a covalent bond, fast optimization of the catalyst system.

The actual catalyst for the allylic substitution consists of an iridium(I)-precatalyst  $\{\text{Ir}(\text{coe})_2\text{Cl}_2\}_2$  and the synthesized ligand. When both compounds are added together the diene moiety of the ligand displaces the cyclooctene ligands of the precatalyst. The active catalyst is expected to catalyze allylic substitutions. In the presence of a chiral source, like DNA, this reaction can be enantioselective.

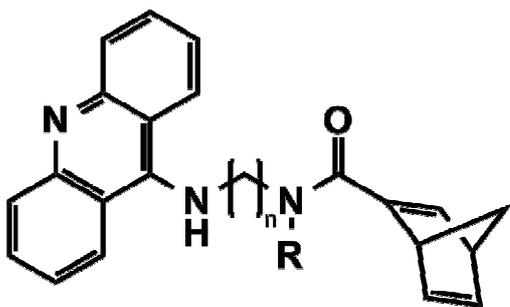


Figure 3; General design of the ligand.

Fig. 3 shows a general design of the ligand to be synthesized. This is based on the first generation ligands as proposed by Roelfes and Feringa in DNA-based catalysis using a copper(II) complex as a transition metal (Fig. 1). The ligand basically consists of three parts: the diene, which is able to coordinate to iridium(I), the linker, to vary the distance to DNA and the acridine, which is known as an intercalator. In 2004, Carreira et al., used diene-based ligands in asymmetric allylic substitutions. Up to >98% ee was obtained applying [2.2.2]bicyclooctadiene.<sup>[11]</sup> In contrast to the diene functionality used by Jäschke, this design relies on an achiral diene moiety. Enantiomeric excess obtained with this system, must be originating from DNA.

By adjusting the R-group to the amide, the coordination of iridium to the diene and the interaction of the ligand with DNA can be influenced. Varying the length of the linker has as a consequence that the distance of the iridium(I) complex to DNA is changed. This can optimize the chiral environment around the transition metal and hence the enantiomeric excesses.

The first approach into the synthesis of this ligand, starts with the diene, followed by the attachment of the linker and the acridine. The addition of the acridine in the last step and not in one of the previous steps, is to avoid challenges in purification steps. Due to the basic character of the acridine, acridine containing molecules are difficult to purify by column chromatography.

After initial investigations, it was found that the diene moiety is unstable when exposed to high temperatures, strong acidic environments or light.

These instability issues eventually lead to a different approach, which is based on a parallel synthesis of the acridine and diene moiety. In the last step both are coupled by a EDC-coupling between the diene and the acridine. This approach was designed in order to prevent degradation in early stages.

## 2. Results and Discussion

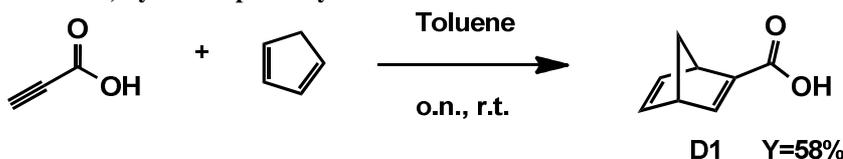
### 2.1 Syntheses of diene-based ligands

The first synthetic pathway begins with the synthesis of the iridium coordinating moiety in the ligand, the diene. Three diene-containing molecules were designed and synthesized during this approach and the results are discussed in this section.

#### 2.1.1 Synthesis of D1

The synthesis of **D1** was done by a Diels Alder cycloaddition reaction between propargylic acid and cyclopentadiene (Scheme 2). An excess (2.5 eq.) of cyclopentadiene was used to increase the rate of formation of the product.

Scheme 2; Synthetic pathway of D1



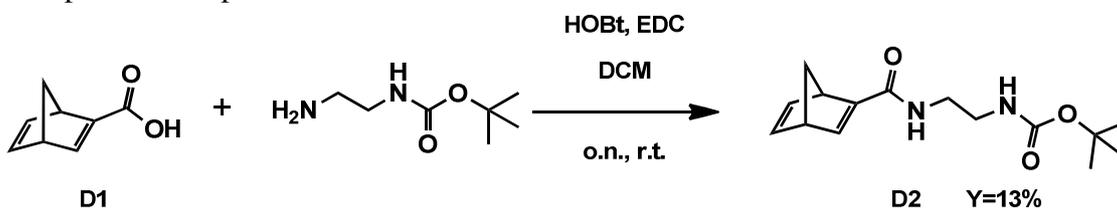
After stirring over night, NMR showed that there was still around 20% propargylic acid present in the solution. By changing the conditions, it might be possible to obtain higher conversions and higher yields. Options are to use a higher excess of cyclopentadiene, increase the reaction time, or to slightly warm the solution. The latter has to be done carefully, because the norbornadiene showed to be sensitive when exposed to high temperatures.

In order to get a higher conversion and to reduce the reaction time, the reaction was also proceeded in the presence of a catalytic amount of aluminum trichloride. Literature showed good results using the methyl ester, because Lewis acid catalysis induced a tremendous rate acceleration.<sup>[12]</sup> Using propargylic acid instead of methyl propiolate did not lead to product formation. Further investigations showed that toluene is not a suitable solvent for this reaction (see section 2.1.3). Using benzene as a solvent might give better results.

The product was initially separated from the substrate by recrystallization from methanol/water, but evaporation of the liquid showed that not all product was crystallized. By treatment of the crude product with pentane, only **D1** dissolved and the substrate (a brownish oil) is left behind. After evaporation, the product was obtained in high purity.

### 2.1.2 Synthesis of D2

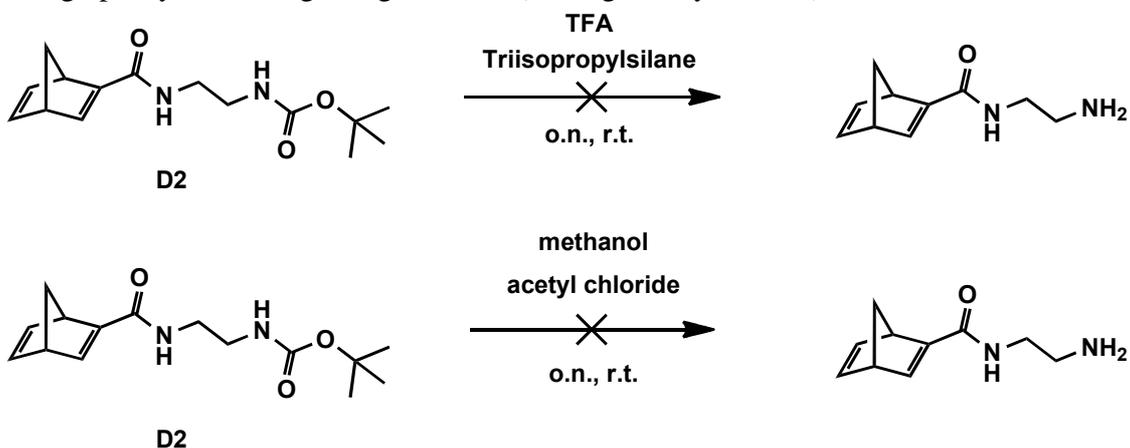
**D2** was obtained after an amide bond forming reaction between **D1** and an excess (1.75 eq.) of N-Boc-ethylenediamine (Scheme 3). One nitrogen of the ethylenediamine was Boc-protected to prevent a reaction on both sides of the molecule.



Scheme 3; Synthetic pathway of D2

HOBt and EDC were added to activate **D1** and therefore make it more reactive. Furthermore EDC reacts with water, originating from **D1**, to form the stable urea. This prevents the equilibrium to go back to the starting material and therefore higher yields are obtained. After **D1** was activated, **D2** was formed via an S<sub>N</sub>2 reaction between the activated variant of **D1** and N-Boc-ethylenediamine.

The yield obtained from this reaction was not very high. This is due to an impurity with a similar R<sub>f</sub>-value compared to the product, which makes it difficult to purify. Various column chromatography's (pentane/ethyl acetate, ethyl acetate) and recrystallizations (ether/methanol, ethyl acetate/pentane) were tried. Eventually, the product was obtained in high purity after using a large column (silica gel, ethyl acetate).



Scheme 4; Attempted deprotection of D2

Unfortunately, there was no way found to remove the protection group and isolate the product. Different methods were tried (Scheme 4). The use of trifluoroacetic acid in combination with triisopropylsilane lead to degradation of the product and no conversion was observed using ethanol/acetyl chloride.<sup>[13]</sup>

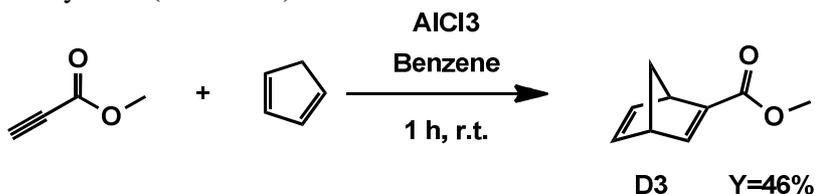
Because of the difficulties that were experienced during the deprotection of the Boc-protected diene and linker, a reaction between **D1** and a large excess (100 eq.) of ethylenediamine was carried out. The large excess of ethylenediamine was present to prevent the formation of disubstituted ethylenediamine.

Unfortunately, no way was found to isolate the product and this synthetic pathway was not further explored.

### 2.1.3 Synthesis of D3

In order to prevent the use of N-Bocethylenediamine, it was tried to use the ester (**D3**) instead of the acid (**D1**) and then attach the linker using an excess of unprotected ethylenediamine and a catalytic amount of sodium cyanide.

At first a reaction between **D1** and methanol, in the presence of a trace of acid, was proceeded, but no product was obtained. Therefore a reaction between methyl propiolate and cyclopentadiene in benzene was carried out, using aluminum trichloride as a catalyst.<sup>[14]</sup> (Scheme 5).

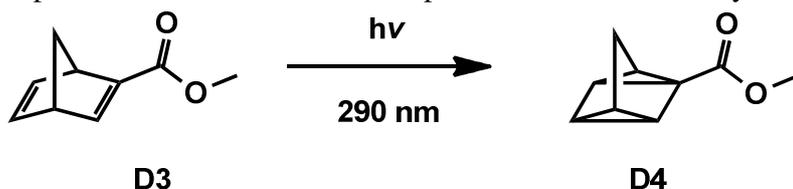


Scheme 5; Synthetic pathway of D3

Also toluene was tested as a solvent, but a side reaction, presumably a Friedel Crafts acylation between toluene and methyl propiolate, lead to a decrease in yield and long and difficult work up.

The reaction was proceeded on both small and large scale. At large scale, a yield of 46% was obtained, but the results of  $^1\text{H}$  NMR indicated the presence of impurities. At small scale the yield was significantly lower (26%), but characterization of the product showed the product was quite pure.

Efforts were made to try and purify the crude product obtained from the large scale, but unfortunately no suitable procedure to purify the crude product was developed. It was found in literature that **D3** can degrade to **D4** under exposure to light.<sup>[15]</sup> This might be an explanation for the difficulties in purification and the low yields that were experienced.



Scheme 6; Photoisomerization of D3 to D4

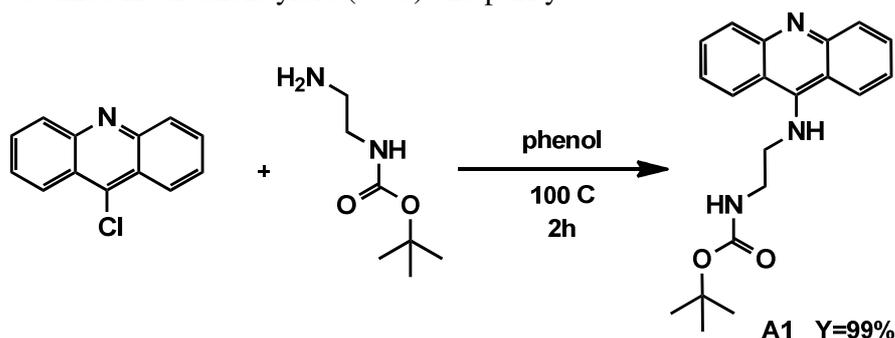
The product obtained from the small scale, was used in the next step, where ethylenediamine was attached to the ester, under presence of a catalytic amount of sodium cyanide. Due to formation of a large amount of byproduct, it was decided to develop a new synthetic pathway and stop trying to increase the purity of the ester.

## 2.2 Syntheses of acridine-based ligands

In order to overcome instability issues originating from diene-containing ligands, a second approach was chosen. Here the synthetic pathway starts with the intercalating ligand and finally attaches the diene functionality. Different structures were developed and the results are discussed in this section.

### 2.2.1 Synthesis of A1

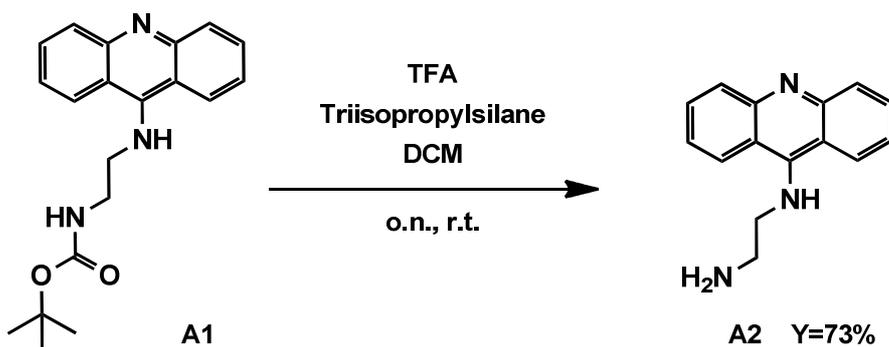
**A1** was obtained by a nucleophilic aromatic substitution reaction between 9-chloroacridine and N-Bocethylenediamine in phenol<sup>[1]</sup> (Scheme 7). The product was obtained in excellent yield (99%) and purity.



Scheme 7; Synthetic pathway of **A1**

### 2.2.2 Synthesis of A2

**A2** was achieved by mixing **A1**, trifluoroacetic acid and triisopropylsilane in CH<sub>2</sub>Cl<sub>2</sub> (Scheme 8). Based on the <sup>1</sup>H NMR spectrum it was assumed that the product was pure enough to be used in the next step without further purifications. Later it turned out that an impurity was visible on TLC which has a similar R<sub>F</sub> value compared to the final product **L1**.



Scheme 8; Synthetic pathway of A2

Therefore it was decided to purify the product by using column chromatography (AlOx neutral akt. I, CHCl<sub>3</sub>/Methanol/Et<sub>3</sub>N 15:1:1). When loading the crude product onto the column, it was noticed the product did not dissolve very well, whereas in pure CHCl<sub>3</sub> solubility was better. Therefore, before proceeding, the structures of both the compound that did dissolve and the compound that did not dissolve were determined with NMR. According to NMR only a small amount of product was present in the liquid and no product at all was present in the solid. This implies that a degradation process had taken place. This was also indicated by a change in properties of the product, which looked more like a powder instead of oil.

It is most likely that the product degraded to acridone, (Fig. 4) by means of a hydrolysis reaction. Signals shown by <sup>1</sup>H NMR at 7.18 and 7.51 and the results from mass spectrometry (m/z=195.06759) confirm this theory.

It was observed that degradation took place more rapidly when the product was exposed to the eluents, consisting of both methanol and triethylamine. It is possible that these solvents increase the rate of degradation.

A downside to this theory is that the sample for mass spectrometry of A2 was prepared in methanol and stayed for a month, but the results of mass spectrometry did not show any sign of degradation. Therefore if the solvent induced degradation it is certain that the presence of a base (triethylamine) plays an important role in this process.

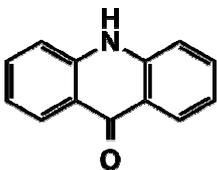


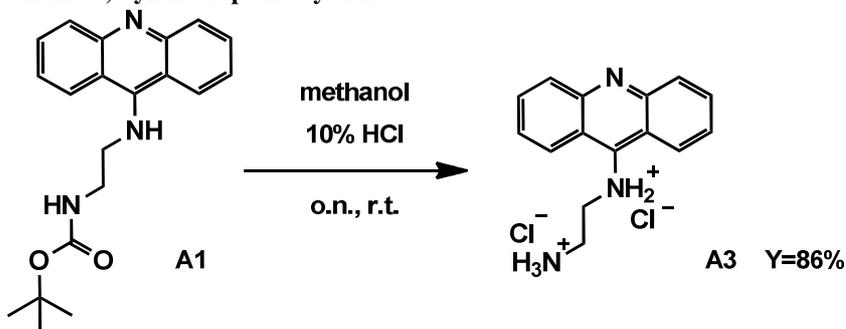
Figure 4; acridin-9(10H)-one (acridone, degradation product)

Due to instability of the A2, the product was not characterized completely, but the results from <sup>1</sup>H NMR and mass spectrometry indicate that the reaction was successful.

### 2.2.3 Synthesis of A3

To prevent the product from degradation **A1** was deprotected by mixing with methanol and 10% HCl, resulting in the salt, which is believed to be more stable than **A2**.<sup>[16]</sup> (Scheme 9).

Scheme 9; Synthetic pathway of A3

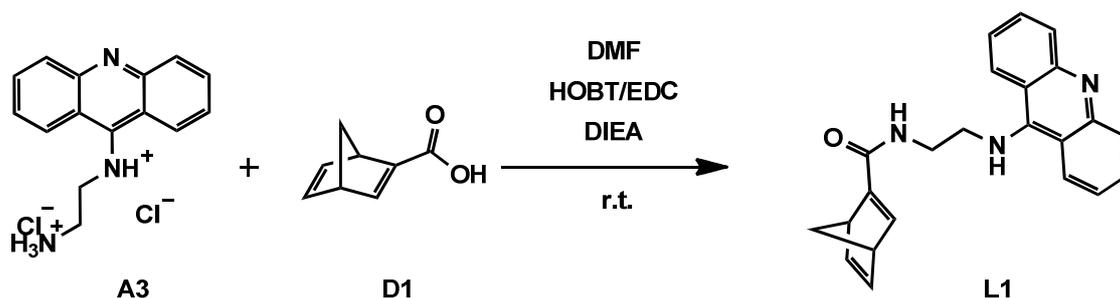


The reaction proceeds in excellent yield (86%) and high purity. NMR showed the existence of both **A3** and the triple protonated variant.

However, the data from mass spectrometry showed the presence of a large amount of acridone. Since neither <sup>1</sup>H NMR or <sup>13</sup>C NMR showed any sign of the presence of acridone, it is certain that degradation had taken place either in the time before the sample was measured or during the measurements. It is remarkable that degradation was not found for the sample of **A2**. A possible explanation can be the presence of HCl. This explanation is not in agreement with the fact that the synthesis of **A3** took place in methanol and 10% HCl and no acridone was formed according to <sup>1</sup>H NMR and <sup>13</sup>C NMR. Presumably, hydrolysis of **A3** in the presence of HCl is a slow process and degradation to acridone takes place after time. It is advised to store acridine-containing ligands under inert atmosphere, to prevent degradation caused by hydrolysis due to moisture from the air.

### 2.2.4 Synthesis of L1

Finally **L1** was produced by connecting **A3** and **D1**. (Scheme 10). First the acid was activated using HOBt and EDC. **A3** was deprotonated by a base (N,N-diisopropylethylamine) (Scheme 10).



Scheme 10; Synthetic pathway of L1

The reaction was also tried using  $\text{CH}_2\text{Cl}_2$  and  $\text{CHCl}_3$  as solvents, but the best results were obtained using DMF.<sup>[17]</sup> The product was not obtained pure, but  $^1\text{H}$  NMR showed the presence of the acridine (7.26-8.14 ppm), the linker (3.16, 3.96 ppm) and the diene functionality (2.05, 3.59, 3.87, 6.81 ppm). The results from mass spectrometry ( $m/z=356.17678$ ) also show the presence of **L1**. No signs of **A2** or the activated ester of **D1** were present, which implies that signals showed by  $^1\text{H}$  NMR must be due to the presence of **L1** and can not originate from the uncoupled (activated) **D1** and **A2**.

It is assumed that **L1** can be isolated using column chromatography (AlOx neutral akt. I,  $\text{CHCl}_3/\text{Et}_3\text{N}$  60:1), if a large column is used and all DMF is evaporated prior to column chromatography. However, no information is known about the stability of **L1** under basic conditions. As it was shown before, acridine-containing ligands can be unstable under basic conditions. If that is also the case for **L1** the proposed eluens ( $\text{CHCl}_3/\text{Et}_3\text{N}$  60:1) is not suitable and another way of purification must be developed. Many other eluens were already tried (acetonitrile/water,  $\text{CHCl}_3/\text{MeOH}/\text{Et}_3\text{N}$ , ethyl acetate/pentane, toluene), but the separation was less efficient.

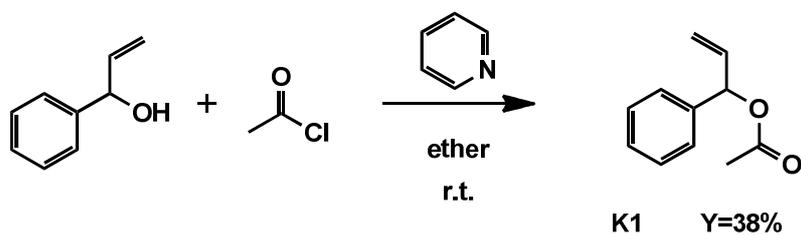
Another possibility to isolate **L1** is using prep-HPLC, but this method is time consuming and has not yet been explored any further.

In order to make **D1** more reactive and therefore increase the reaction rate and improve the yield, **D1** was reacted with thionyl chloride in toluene to obtain an acid chloride. Unfortunately, no product was isolated probably due to sensitivity of **D1** to strong acidic environments.

### 2.3 Synthesis of substrate for Ir-catalyzed reaction

Asymmetric allylic amination of phenyl allyl acetate was already catalyzed successfully by a DNA-based catalyst.<sup>[8]</sup> It is therefore an excellent benchmark reaction testing the catalytic properties of the new DNA-based system.

### 2.3.1 Synthesis of K1



Scheme 11; Synthetic pathway of K1

**K1** was obtained by mixing  $\alpha$ -vinylbenzyl alcohol with acetyl chloride and pyridine in ether. (Scheme 11). Preliminary results gave a yield of 38%, but this could be optimized.

### 3. Conclusion and Perspectives

It was showed that both structures **D1** and **A3** can be synthesized in satisfying yields. Full characterization of the structures showed both were obtained completely pure.

It was also demonstrated that ligand, **L1**, can be obtained by coupling **D1** and **A3** in DMF under presence of HOBt/EDC and diisopropylethylamine. A possible way of purifying the crude product, is by using a large column (AlOx neutral akt. I, CHCl<sub>3</sub>/Et<sub>3</sub>N). However, it is unknown whether **L1** remains stable under these circumstances. Another way to isolate **L1** is using prep-HPLC, but this method has not been explored any further. Many difficulties have been experienced during the synthesis of **L1**. The diene-containing functionalities showed to be very sensitive to light, heat and strong acidic environments. It is therefore advised to attach the diene not before the last step.

The acridine-containing molecules also showed some instability issues. Degradation to acridone can take place by means of a hydrolysis reaction in both acidic and basic environments. Therefore it is advised to store acridine-containing ligands under an inert atmosphere, to prevent degradation to acridone.

Future work will mainly focus on isolating **L1**. When this has succeeded, **L1** can be used together with an iridium(I) complex and DNA as an enantioselective catalyst in asymmetric allylic substitutions.

The structure of **L1** can be optimized by adjusting the spacer length and/or adding an extra group at the amide (Fig. 3), in order to obtain better enantioselectivities.

## 4. Experimental Section

### *(1R,4S)-bicyclo[2.2.1]hepta-2,5-diene-2-carboxylic acid (D1)*

To a solution of 1,4 g (20 mmol) of propargylic acid in 30 ml of toluene was added 3,31 g (50 mmol) of cyclopentadiene at 0°C. The mixture was allowed to stir overnight at room temperature. The mixture was cooled to 0°C and a solution of sodium carbonate in water (3,5 g/35 ml) was slowly added. The aqueous phase was extracted with 3 x 20 ml of ethyl acetate. Then the aqueous phase was acidified to pH~1 at 0°C with concentrated HCl and the aqueous phase was extracted with 3 x 20 ml of ether. The combined organic layers were dried over sodium sulfate and the solvent was evaporated. The crude product was purified by recrystallization from methanol/H<sub>2</sub>O to give **D1** as white crystals. Yield=1,776 g (57%), Mp=86.1-89.6°C, HMRS (ESI) calcd for C<sub>8</sub>H<sub>7</sub>O<sub>2</sub>: 135.04406 ([M-H<sup>+</sup>]), found 135.04520

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ(ppm)= 2.15 (dd, 2H, J<sub>1</sub>=5.76 Hz, J<sub>2</sub>=13.39 Hz), 3.72 (m, 1H), 3.88 (m, 1H), 6.71 (dd, 1H, J<sub>1</sub>=3.23 Hz, J<sub>2</sub>=4.62 Hz), 6.91 (dd, 1H, J<sub>1</sub>=3.19 Hz, J<sub>2</sub>=4.95 Hz), 7.80 (d, 1H, J=3.25 Hz)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz) δ(ppm)= 49.99, 52.08, 74.71, 141.76, 144.02, 149.28, 159.37, 160.40

### *Tert-butyl (2-((1R,4S)-bicyclo[2.2.1]hepta-2,5-diene-2-carboxamido)ethyl)carbamate (D2)*

Under nitrogen atmosphere 1,261 g (9,26 mmol) of **D1** was dissolved in 20 ml of CH<sub>2</sub>Cl<sub>2</sub>. 1,78 g (9,26 mmol) EDC and 1,1 g (8,12 mmol) HOBt were added at 0°C. After 1 hour, 2,60 g (16,21 mmol) of N-Boc-ethylenediamine was added and the mixture was allowed to warm up to room temperature and was stirred overnight. The mixture was washed with saturated sodium bicarbonate and brine. The organic phase was dried over sodium sulfate and the solvent was evaporated. After column chromatography (silica gel, ethyl acetate) **D2** was obtained as a yellowish solid. Yield=13%, Mp=130.6-133.3°C, HMRS (ESI) calcd for C<sub>15</sub>O<sub>3</sub>N<sub>2</sub>H<sub>22</sub>: 301.15281 ([M+Na<sup>+</sup>]), found 301.15106

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz) δ (ppm)= 1.40 (s, 9H), 2.05 (dd, 2H, J<sub>1</sub>=6.36 Hz J<sub>2</sub>=6.42 Hz), 3.28 (m, 2H), 3.36 (m, 2H), 3.64 (m, 1H), 3.85 (m, 1H), 5.09 (s, 1H), 6.64 (s, 1H), 6.70 (dd, 1H, J<sub>1</sub>=3.23 Hz, J<sub>2</sub>=4.87 Hz), 6.85 (dd, 1H, J<sub>1</sub>=3.23 Hz, J<sub>2</sub>=4.70 Hz), 7.28 (d, 1H, J=2.86 Hz)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz) δ (ppm)= 28.35, 40.02, 41.30, 50.16, 51.30, 74.02, 79.72, 142.20, 143.16, 148.75, 152.60, 157.29, 165.46

### *(1R,4S)-methyl bicyclo[2.2.1]hepta-2,5-diene-2-carboxylate (D3)*

The procedure was adapted from Fieneman et al.<sup>[14]</sup>

Under nitrogen atmosphere 3,97 g (30 mmol) of aluminum trichloride was dissolved in benzene. 5 g (59 mmol) of methyl propiolate was added and the mixture was cooled to

0°C. 3,93 g (59 mmol) of cyclopentadiene was added drop wise and the mixture was shielded from the light to prevent photoisomerization. After 1 hour the mixture was poured in a saturated aqueous solution of sodium bicarbonate. Ether was added to the mixture and it was washed with water. The combined organic layers were dried over magnesium sulfate. After evaporation of the solvent, the crude product was purified by column chromatography (silica gel, toluene) and gave 4,028 g (46%) of a colorless liquid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ (ppm)= 1.54 (s, 3H), 2.11 (dd, 2H, J<sub>1</sub>=5.68, J<sub>2</sub>=10.67), 3.69 (m, 1H), 3.88 (m, 1H), 6.71 (dd, 1H, J<sub>1</sub>=3.29 Hz, J<sub>2</sub>=4.90 Hz), 6.88 (dd, 1H, J<sub>1</sub>=3.11 Hz, J<sub>2</sub>=5.07 Hz), 7.62 (d, 1H, J=3.22 Hz)

#### *Tert-butyl (2-(acridin-9-ylamino)ethyl)carbamate (A1)*

The procedure was adapted from Roelfes et al.<sup>[11]</sup>

Under a nitrogen atmosphere 1 g (4,68 mmol) of 9-chloroacridine, 1 g (6,24 mmol) of N-Boc-ethylenediamine and about 5 g of phenol were added to a three-necked-flask and the whole was stirred for 2 hours at 100°C. Ether was added to the flask and the mixture was stirred for 1 hour. The ether was decanted and fresh ether was added. This procedure was repeated a couple of times until all the phenol was removed. The suspension was filtered and washed with ether and gave 1,557 g (99%) of bright yellow crystals. Mp=214.4-214.6, HMRS (ESI) calcd for C<sub>20</sub>O<sub>3</sub>N<sub>3</sub>H<sub>24</sub>: 338.18630 ([M-H<sup>+</sup>]), found 338.18569

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ (ppm)= 1.46 (s, 9H), 3.85 (m, 2H), 4.27 (m, 2H), 6.61 (m, 1H), 7.13 (dd, 2H, J<sub>1</sub>=7,62 Hz, J<sub>2</sub>=7,62 Hz), 7.38 (dd, 2H, J<sub>1</sub>=7.63. Hz, J<sub>2</sub>=7.63 ), 8.09 (d, 2H, J=8.47), 8.30 (d, 2H, J=8.47)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 200 MHz) δ (ppm)= 28.48, 39.96, 51.76, 80.54, 112.14, 119.49, 123.30, 124.91, 133.94, 139.56, 156.82, 158.49

#### *N<sup>1</sup>-(acridin-9-yl)ethane-1,2-diamine (A2)*

To a solution of 300 mg (0,89 mmol) of **A1** in 10 ml CH<sub>2</sub>Cl<sub>2</sub> was added 1,52 g (13,33 mmol) of trifluoroacetic acid and 1 ml of triisopropylsilane. The mixture was allowed to stir overnight at room temperature. 1M HCl was added and the CH<sub>2</sub>Cl<sub>2</sub> was evaporated. The mixture was extracted with ether. The pH of the aqueous layer was brought to >10 by addition of 2M NaOH (aq) and the aqueous layers were extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layers were dried over sodium sulfate. The solvent was evaporated and 153 mg (73%) of product was obtained as a sticky yellow oil/solid. HMRS (ESI) calcd for C<sub>15</sub>H<sub>16</sub>N<sub>3</sub>: 338.13387 ([M+H<sup>+</sup>]), found 338.13390

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ (ppm)= 2.70 (s, 1H), 2.98 (m, 2H), 3.77 (m, 2H), 4.11 (s, 1H), 7.31 (m, 2H), 7.62 (m, 2H), 8.03 (d, 2H, J=8.65 Hz), 8.14 (d, 2H, J=8.72 Hz)

#### *N<sup>1</sup>-(aridin-9-yl)ethane-1,2-diaminium chloride (A3)*

The procedure was adapted from Csuk et al.<sup>[16]</sup>

500 mg (1,48 mmol) of **A1** was dissolved in 22,3 ml methanol. 2,3 ml of 10% HCl was added and the mixture was allowed to stir overnight at room temperature.

The solvents were evaporated and 394 mg (86%) of product was obtained as a bright yellow salt. Mp=281.4-282.4, HMRS (ESI) calcd for C<sub>15</sub> H<sub>16</sub>N<sub>3</sub> (-2HCl): 338.13387 ([M+H<sup>+</sup>]), found 338.13335

<sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ (ppm)= 3.40 (t, 2H, J<sub>1</sub>=6.25 Hz, J<sub>2</sub>=6.25 Hz), 4.27 (t, 2H, J<sub>1</sub>=6.30 Hz, J<sub>2</sub>=6.30 Hz), 7.41 (dd, 2H, J<sub>1</sub>=7.80 Hz, J<sub>2</sub>=7.80 Hz), 7.56 (d, 2H, J=8.54 Hz), 7.80 (dd, 2H, J<sub>1</sub>=7.89 Hz, J<sub>2</sub>=7.89 Hz), 8.13 (d, 2H, J=8.80 Hz)

*9-((2-ammonioethyl)ammonio)acridin-10-ium chloride (A3)*

<sup>1</sup>H NMR (D<sub>2</sub>O, 200 MHz) δ (ppm)= 3.47 (t, 2H, J<sub>1</sub>=6.47 Hz, J<sub>2</sub>=6.47 Hz), 4.24 (t, 2H, J<sub>1</sub>=6.49 Hz, J<sub>2</sub>=6.49 Hz), 7.41 (d, 2H, J=8.49 Hz), 7.47 (m, 2H), 7.84 (m, 2H, J<sub>1</sub>=6.99 Hz, J<sub>2</sub>=8.26 Hz), 8.02 (d, 2H, J=8.67 Hz)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 200 MHz) δ (ppm)= 38.16, 45.27, 111.49, 118.14, 124.16, 135.34, 138.60, 157.16, 202.04

*N-(2-(acridin-9-ylamino)ethyl)bicyclo[2.2.1]hepta-2,5-diene-2-carboxamide (L1)*

The procedure was adapted from Šebestík et al.<sup>[17]</sup>

Under a nitrogen atmosphere 20,6 mg (0,152 mmol) of **D1** was dissolved in 2 ml DMF. 20.5 mg (0,152 mmol) of HOBT, 29,1 mg (0,152 mmol) of EDC and 19,6 mg (0,152 mmol) of *N,N*-diisopropylethylamine were added at 0°C. The mixture was stirred for one hour, then 32 mg (0,103 mmol) of **A3** was added, accompanied with 39,2 mg (304 μmol) *N,N*-diisopropylethylamine. Ethyl acetate was added and the mixture was washed with sodium hydrogen carbonate. The organic phase was dried over sodium sulfate and the solvent was evaporated. The mixture was purified by column chromatography (AlOx neutral akt. I, CHCl<sub>3</sub>/Et<sub>3</sub>N 60:1). The phases containing the product were extracted with water. Then the organic phase was washed with an HCl solution of pH=3. To the aqueous phase an aqueous solution of NaOH was added, until the pH was >10. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layers were dried over sodium sulfate and the solvent was evaporated. The crude product was characterized. HMRS (ESI) calcd for C<sub>23</sub> H<sub>22</sub>O<sub>1</sub>N<sub>3</sub>: 356.17574 ([M+H<sup>+</sup>]), found 356.17678

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ (ppm)= 2.05 (m, 2H), 3.16 (m, 2H), 3.59 (m, 1H), 3.87 (m, 1H), 3.96 (t, 2H, J<sub>1</sub>=5.22 Hz, J<sub>2</sub>=5.22 Hz), 4.73 (m, 1H), 6.48 (m, 1H), 6.66 (m, 1H), 6.81 (m, 2H), 7.26 (m, 2H), 7.55 (m, 2H), 8.05 (d, 2H, J=8.69 Hz), 8.14 (d, 2H, J=8.64 Hz)

*1-phenylallyl acetate (K1)*

Under a nitrogen atmosphere 500 mg (3,726 mmol) of α-vinylbenzylalcohol and 354 mg (4,472 mmol) of pyridine were dissolved in dry ether. 351 mg (4,472 mmol) of acetyl chloride were added slowly and the reaction was stirred at room temperature. The conversion was checked by TLC. When the reaction was finished, the mixture was

washed with a saturated ammonium chloride solution and brine. The organic phase was dried over sodium sulfate and the solvent was evaporated. The crude product was purified by column chromatography (silica gel, pentane/ether 10:1). The product was obtained as a colorless liquid (0,298 g, 38%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ (ppm)= 2.10 (s, 3H), 5.25 (m, 2H), 5.99 (m, 1H), 6.25 (m, 1H), 7.30 (m, 5H)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 200 MHz) δ (ppm)=21.24, 76.21, 116.19, 127.17, 128.19, 128.26, 128.58, 129.06, 136.32, 138.92, 169.94

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