Enantio- and Stereo-Selective Studies in the Asymmetric Hydrogenation of Cyclohexenes by Iridium Catalysis

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Graduation report

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Abstract in Dutch

Het onderzoek beschreven in deze scriptie richt zich op de asymmetrische hydrogenering van cyclohexadienen tot chirale cyclohexanen. Via een regioselectieve kobalt gekatalyseerde Diels-Alder reactie zijn 1,3-gesubstitueerde cyclohexenen gesynthetiseerd. Deze cyclohexenen dienen als substraten voor de asymmetrische hydrogenering. De asymmetrische hydrogenering wordt gekatalyseerd met N,P-ligand gecoördineerde iridium complexen. De complexen hebben een imidazol basis structuur. Aan een sterische groep, direct gebonden aan de imidazol basis, zijn modificaties gemaakt om de sterische en elektronische aard van de katalysatoren te bestuderen. De gehydrogeneerde substraten zijn geanalyseerd op de conversie tot het product, de enantiomeric excess (ee) en de cis/ trans-ratio. Een zeer grote hoeveelheid substraten zijn succesvol gesynthetiseerd en met goede resultaten gehydrogeneerd met een gemodificeerde, meer sterisch gehinderde, katalysator. Verder bleek een gemodificeerde katalysator met een sterk elektron inducerend effect geschikt voor een substraat waar elke katalysator in de onderzoeksgroep bij faalde. Een nieuwe, meer sterisch gehinderde, katalysator bleek verder geschikt voor de selectieve hydrogenering van sterisch gehinderde of sterk coördinerende cyclohexadienen. De producten zijn chirale cyclohexenen met uitstekende resultaten (99% ee).

Acknowledgements

I want to thank a number of people who helped me with my research, writing my thesis and supervising me. First prof. Pher G. Andersson for giving me the chance to work in his group and accepting me as a future student. Under his supervision I have learned a lot of knowledge and insight in organic chemistry.

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Abbreviations

^{1}H NMR	-	Proton Nuclear Magnetic Resonance
^{13}C NMR	-	Carbon-13 Nuclear Magnetic Resonance
Ar	-	Aryl group
BAr_F	-	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
bpy	-	2,2-bipyridine
COD	-	Cyclooctadiene
DCM	-	Dichloromethane
ee	-	Enantiomeric Excess
EtOAc	-	Ethyl Acetate
HPLC	-	High Performance Liquid Chromatography
HRMS	-	High Resolution Mass Spectrometry
IR	-	Infrared Spectrometry
MeOh	-	Methanol
Pd/C	-	Palladium on Carbon
Ph	-	Phenyl group
TFA	-	Trifluoroacetic acid
THF	-	Tetrahydrofuran
TLC	-	Thin Layer Chromatography
TsCl	-	4-toluenesulfonyl chloride
UV/VIS	-	Ultra-Violet Visible

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1.0 Introduction

1.1. A brief introduction in stereochemistry and chirality

A compound with the molecular formula C_4H_{10} can have two structures, namely the linear butane form and the isomer of butane called iso-butane. Although both compounds have the same molecular formula they are different (Figure 1.1 a). These are called constitutional isomers. Next to constitutional isomers there are stereoisomers. Stereoisomers are molecules were the atoms adjacent to a double bonded carbon bond have a different arrangement. In case of the arrangement were both hydrogens are on the same side of the molecule it is called cis-configuration and when the hydrogens are on opposite side the molecule has the so called trans-configuration. It is however not a requirement that the attached atoms are hydrogens.

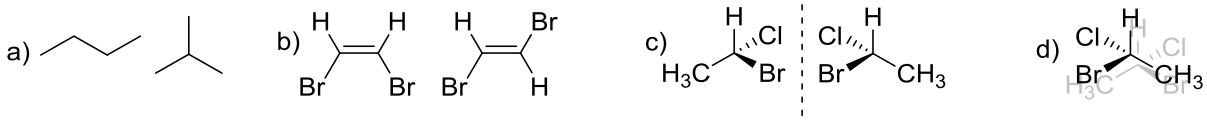


Figure 1.1. a) Constitutional isomers of C_4H_{10} butane and 2-methyl-butane, b) Stereoisomers cis-1,2-dibromo-ethene and trans-1,2-dibromo-ethene, c) Non-superposable mirror images of 1-bromo-1-chloro-ethane, d) Overlap of both non-superposable mirror images.

Stereoisomers have two subgroups called, diastereomers and enantiomers. Consider the molecule with formula C_2H_4BrCl. The molecule is substituted with four different atoms. There are two ways to rearrange the atoms on the central carbon. Both ways have the same connectivity but a different arrangement on the central carbon. Despite having the same connectivity, these molecules are in fact different since the one cannot be superimposed on the other, however, can be to the mirror image of the other. As a result of this, these molecules are referred to as being *chiral*, furthermore, as *enantiomers* of one another (Figure 1.1 c and d). The term non-superimposable is best described with two hands (Figure 1.2). A left and a right hand are mirror images of each other but once you overlap them you see they are different from each other and are non-superimposable.

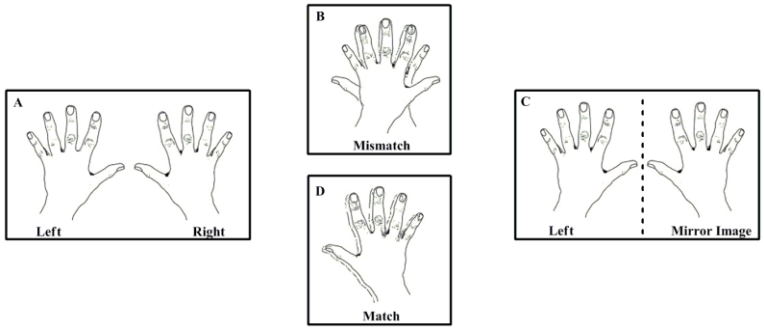


Figure 1.2. Non-superimposable explained by left and right hand (A) that are mirror images of each other(C) but cannot be fit on top of each other (B). A right hand can however fit on a right hand (D) and thus is the same[1].

A compound can have more than one chiral center that results in multiple isomers being formed. The number of different possibilities is given by 2^n where n stands for the number of chiral stereocenters. Diastereomers are molecules with multiple chiral centers that are not mirror images of each other (Figure 1.3)

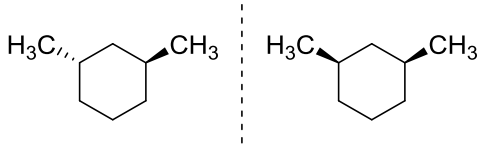


Figure 1.3. Diastereomers of 1,3-dimethyl-cyclohexane, trans (left) and cis (right).

Two enantiomers of a molecule have the exact same physical properties and even normal spectrometry cannot distinguish between them. The only method to distinguish between them is by measuring the bending of plane-polarized light by the compound, its optical activity. Each enantiomer bends the plane-polarized light beam either clockwise (+) or counter clockwise (-) depending on the enantiomer. By determining the amount of bending, the specific rotation of the enantiomer can be determined and the enantiomers can be distinguished from one another.

Different enantiomers of a molecule can have different reactivity's in a chiral environment. One enantiomer can react, activate or give a different biological effect than the other enantiomer. A good example of the different effects of enantiomers is limonene. When the nose smells limonene the odor depends on the enantiomer. The (S)-enantiomer gives a spearmint odor while the other (R)-enantiomer gives a lemon-like odor[2] (Figure 1.4 a).

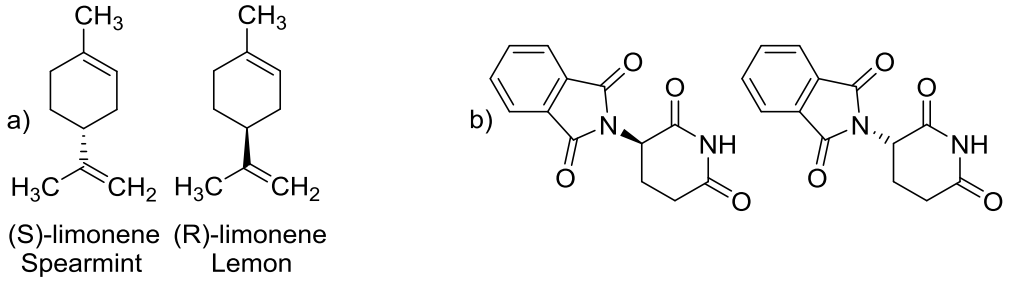


Figure 1.4.a) Enantiomers of limonene and the odor of each enantiomer, b) Both enantiomers of thalidomide.

Another example of the different effects of enantiomers is the Softenon[3] (thalidomide Figure 1.4 b). During the 1950s, Softenon was prescribed to pregnant woman to treat morning sickness. It was sold as a 1:1 mixture of the (*R*) and (*S*) enantiomers (a *racemate*). Unfortunately, one of these enantiomers also caused birth defects in the children of the woman taking Softenon, emphasizing the need for chiral drugs to be sold as single enantiomers. Fortunately, a vast number of reactions that gives a chemist control of the chiral outcome of a reaction, have been developed.
One such reaction is asymmetric hydrogenation, which in combination with iridium complexes, is the focus of this project.

1.2 The project

The main goal of the project is to create a facile, and enantioselective strategy to prepare chiral 1,3-substituted cyclohexanes. This will be done through the asymmetric hydrogenation of 1,3-cyclohexadienes using, predominantly rationally designed imidazole-based iridium catalysts (see Figure 1.6 a).[5]

These chiral cyclohexanes and their preparation can perhaps solve future problems in industries where complete control of chiral molecules is mandatory, like the pharmaceutical industry and agrochemical industry.

The hydrogenations will be carried out with the previously reported imidazole-based catalyst and a thiazole-based catalyst (Figure 1.6 b) from the PGA-group's catalyst library[4,5]. Furthermore, the aryl substituent on the imidazole will be modified in order to evoke higher enantioselectivity (Figure 1.6 c).

The substitutions introduced to the catalyst will study both the steric effects and the electronic effects of ortho and/or para-substituted aryl rings tethered to the imidazole in an effort to boost catalytic efficiency in the hydrogenation of the cyclohexene derivatives (see Figure 1.6 c).

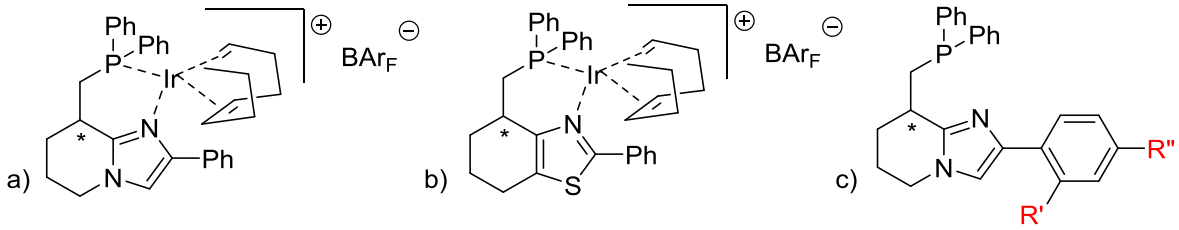


Figure 1.6. a) Previously reported imidazole catalyst, b) Previously reported thiazole-catalyst and c) Substituted imidazole catalyst R´ and R" can either be H, MeO, F, CF_3 or Me.

1.3 Introduction to hydrogenation and catalysis

In a hydrogenation a π-bond is reduced to a sigma bond by addition of H_2 (Figure 1.7). Hydrogenations require a source of hydrogen which can be H_2 gas or another source of non-gaseous hydrogen in which case the reaction is called transfer hydrogenation. Next to the hydrogen source the reaction also requires a form of catalyst like palladium on carbon (Pd/C). The catalyst is used to speed up a reaction while the catalyst itself is regenerated in the end of the reaction instead of being consumed in the process.

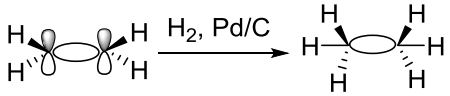


Figure 1.7. An ethene molecule drawn with the molecular orbitals between the carbons.

There are two major forms of chemical catalysis, namely homogeneous catalysis and heterogeneous catalysis[6]. In the former the catalyst is in the same phase as the solvent and the reactants. The reactivity and selectivity of the catalyst is usually very good. The catalysts used in this project are homogeneous. In heterogeneous catalysis the catalyst is in another phase than the solvent. In most cases this means that the catalyst remains insoluble in the solvent. Therefor the reaction will proceed on the surface and in many cases has a lower reaction rate than homogeneous catalysis. However the catalyst can be recovered

easily from the reaction and can be recycled. An example of a heterogeneous catalyst is palladium on carbon.

1.4 Common metals used in asymmetrical hydrogenation

The most common elements used for hydrogenations catalysts are ruthenium, rhodium and iridium. These elements all belong to the "platinum group metals" together with platinum, palladium, and osmium[7]. The elements in this group differ from the normal transition state metals in the fact that they can form more often stable unsaturated 16 electron complexes than the other transition metals that usually form stable 18 electron complexes. Since the 16 electron complexes have a square planar shape they can easily be engaged by other molecules forming complexes that can undergo very unique chemistries [8].

Transition metals in period 6, have lower nuclear charges which stabilizes the electrons in the coherent orbitals making them more stable against oxidations.

As a result, iridium is more prone to forming-softer complexes than rhodium that has more affinity for harder complexes. This is seen in the substrates that each of the complexes has more affinity for. The substrates that rhodium-complexes are used for in the hydrogenation, require a strong electron withdrawing group like a carbonyl, ester or amine-group close to the carbon-carbon π-bond. While these groups form irreversible bonds with the corresponding, ~~a~~ softer iridium hydrogenation complexes. Iridium prefers substrates with a medium electron withdrawing group like an aromatic ring or electron withdrawing group farther away from the carbon-carbon π-bond that will not affect iridium by forming irreversible bonds[9]. The olefins of the substrates used in this project are minimally functionalized which makes iridium the metal of choice.

1.5 A Closer look at the Ligand:

The metal should have an small open site to coordinate to the olefin after it has taken up H_2. The site is created by the addition of ligands which are bulky and block large parts of the catalyst with the steric hindrance. The ligand is bond to iridium by an overlap of the orbitals from two hetero atoms of the bidentate ligand (N,P) in one of the d-orbitals of iridium to form the catalyst with a square planar geometry.

In the ligand (Figure 1.6 a) there are some important features to explain: The chiral center, marked with an asterisk, which is used as the source of chiral information to be passed to the substrate. The chiral center is in the backbone of the ligand (piperidine-ring). This backbone is thus entirely responsible for the enantioselectivity. The heterocycle is used to bind the ligand to iridium which is also the case for the phosphorus atom. The bulky groups attached to phosphine are to create steric hindrance. The selectivity model[10] that shows this is shown in Figure 1.8 a. The alkene will be coordinated to iridium at the crosshair. The parts of the catalyst that have been drawn red are bulky and directs the hydrogenation towards one enantiomer of the products and preferentially the trans-isomer.

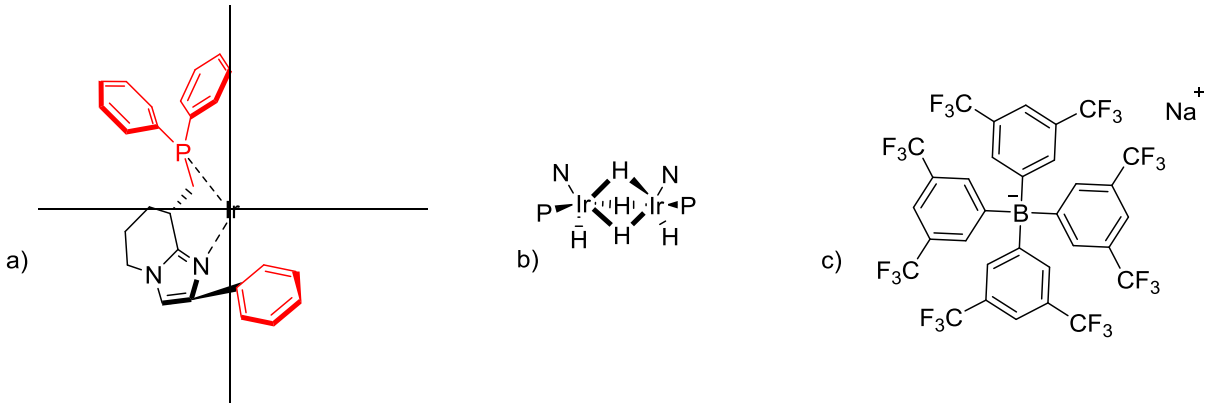


Figure 1.8. a) Selectivity model for the (S)-catalyst; the red color describes the steric hinderance, b) Dimeric hydride structure with two iridium complexes, c) NaBAr$_F$ structure.

These catalysts have been shown to be highly active in the hydrogenation of minimally functionalized olefins. However, these iridium complexes with P,P-ligands and N,P-ligands can form fast and irreversible dimeric and trimeric hydride species (Figure 1.8 b), a bulky and extremely weak coordinating counter-ion like tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BAr$_F$), is introduced to the catalyst to help prevent or hamper this formation[10] (Figure 1.8 c). In addition to this the olefin coordination bonding ability of the complex also increases because of the BAr$_F$ anion.

1.6 Mechanism of N,P-iridium-catalyzed hydrogenation

The mechanism[11] for the iridium N,P-ligand catalyzed hydrogenation is shown in Figure 1.9. The mechanism for the (III/V) catalytical cycle is: First the cyclooctadiene (COD) is hydrogenated and replaced for two solvent molecules and two hydrogen atoms. The oxidation state of iridium is now (III) instead of (I). Coordination of H_2 and an alkene follows while the solvents molecules dissociate. Oxidative insertion of the H_2 where iridium gains the oxidation state of (V). Reductive elimination occurs where the alkane is liberated and two solvents molecules are being taken up to regenerate the first step of the catalytic cycle.

The mechanism for the (I/ III) catalytical cycle is: oxidative addition of H_2 gives Ir(III)-dihydride. The double bond in the substrate is coordinated to iridium and in doing so replaces a solvent molecule. A migratory-insertion of the double bond in the Ir(III)-hydride bond takes place. After a reductive elimination the product is formed an iridium is reduced to Ir(I) that can be oxidized by H_2 to return in the first step. of the circle.

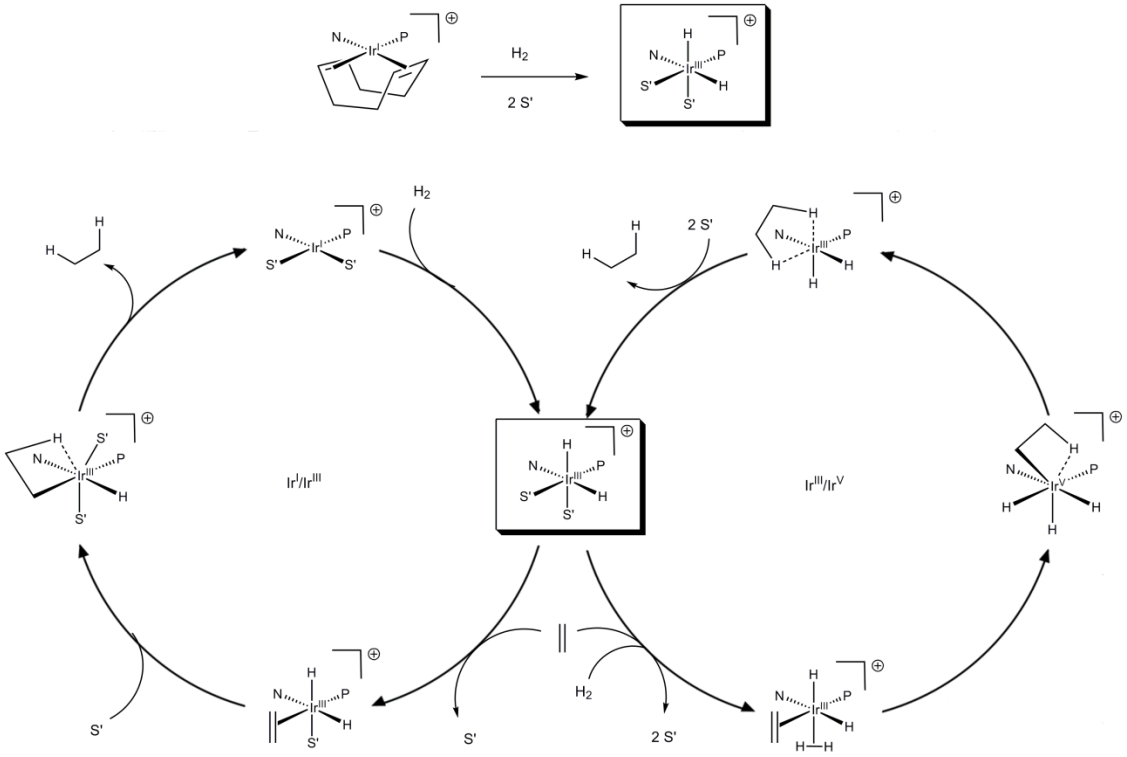


Figure 1.9. Catalytic cycle[2] for the hydrogenation of an alkene by the iridium (III)/iridium (V) mechanism proposed for iridium N,P-complexes by Andersson et al.

1.7 N,P-chelated ligand synthesis

The ligands are synthesized mainly according the procedure published by the PGA-group[5]. It is adjusted in one step (see Results and Discussion section: Ligand Synthesis) where it is needed. In Figure 1.10 the overall synthesis steps are shown. The first four steps are performed towards the full catalysts while the other steps were performed by other group members. The asterisk shows the pure enantiomer separated by preparative High Performance Liquid Chromatography (HPLC) on chiral separation phase. Compounds are collected after they are detected by Ultra Violet/ Visible Light (UV/VIS) detector.

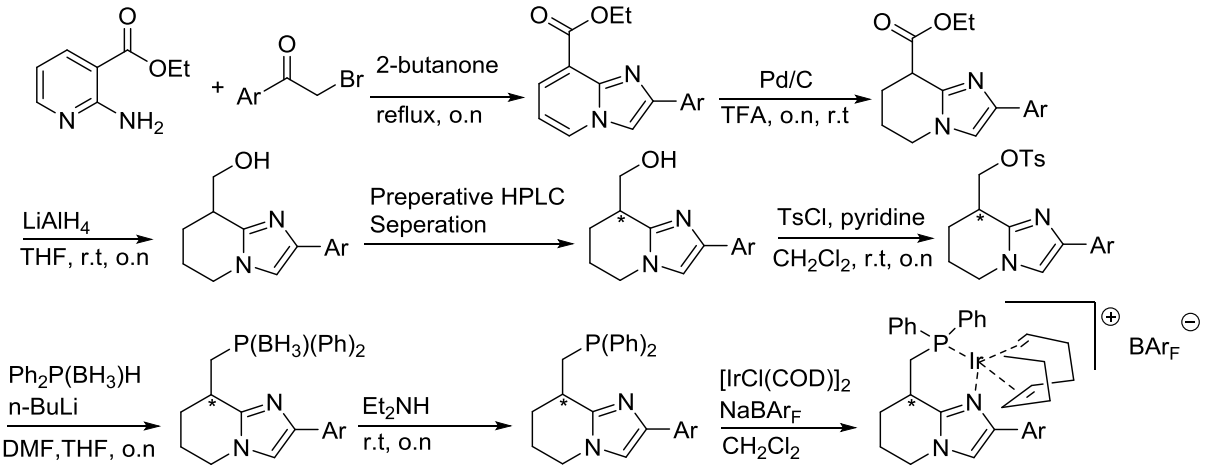


Figure 1.10. Overal steps of the ligand synthesis according to the previous published imidazole iridium-complex catalyst. The Ar group is ortho or/and para: MeO, CH_3, CF_3, Me, F.

Each intermediate of the multi-step synthesis will be fully characterized with Proton Nuclear Magnetic Resonance (^{1}H NMR), Carbon-13 Nuclear Magnetic Resonance (^{13}C NMR), Infrared Spectrometry (IR), Mass Spectrometry (HRMS), Thin Layer Chromatography (TLC), in case of a solid the melting point will be determined and the specific rotation will be determined after the chiral separation step for each intermediate with a polarimeter.

1.8 *meta*-Directed Substrate Synthesis

There are multiple methods known to create cyclohexadienes. Among the popular methods are without a doubt the Birch-reaction which uses lithium or sodium in ammonia to reduce an aromatic ring to a cyclic diene. Another method is the Diels-Alder reaction which can create a cyclic diene from a cyclic or linear 1,3-diene and a dienophile. In this project the Diels-Alder reaction will be used to create the cyclic dienes from a diene and a dienophile with a triple bond (Figure 1.11a).

As is seen in Figure 1.11a the reaction with a substituted diene gives two products. One is the 1,3-product while the other one is the 1,4-product. It is of great importance that only the 1,3-product is formed. When hydrogenated this can result in up to four enantiomers. When the 1,4-product is hydrogenated, the plane of symmetry will go through the bonds of R' and R" create a symmetrical meso compound (Figure 1.11 b.) and thus non chiral.

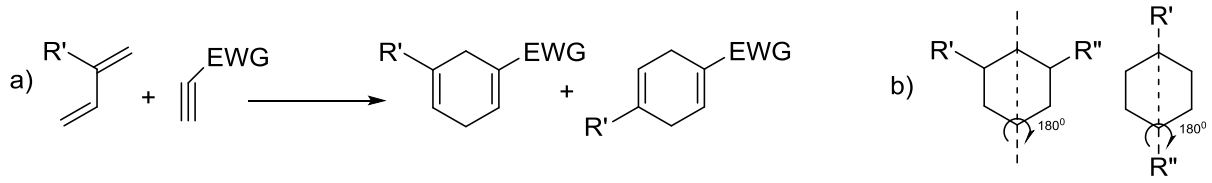


Figure 1.11. a) Diels-Alder reaction of a conjugated diene with an acetylene that has an electron withdrawing group attached, b) Plane of symmetry shown of an 1,3-cyclohexane and a 1,4-cyclohexane.

There are just a few methods reported for a selective 1,3-Diels-Alder reaction (source: Scifinder). The most promising is reported by Hilt *et al*[12]. In this reaction a cobalt 2,2-bipyridine (bpy) complex is used for the promotion of the 1,3-direction (Figure 1.12 a). The complex is activated in-situ to $CoBr(ligand)^+$ and reduced to $Co(ligand)^+$ with zinc iodide and zinc dust. Iron dust is used in this reaction to overcome the (2+2+2) cyclotrimerization product of three alkyne molecules which also can be formed with the same reagents[12] (Figure 1.12 b).

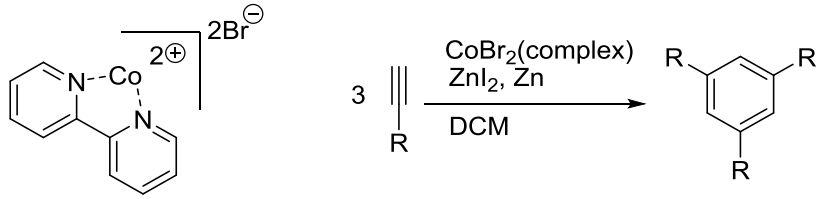


Figure 1.12. a) $CoBr_2$(bpy) complex, b) Formation of the 2+2+2 cyclotrimerization product.

In Figure 1.13 the catalytic cycle of the Cobalt-catalyzed Diels-Alder is shown. In the catalytic cycle there are two pathways to form the [Co(bpy)(alkyne)(diene)] transition state. First a diene is coordinated by replacing two solvent molecules after which the alkyne will replace a solvent molecule. The other pathways is the opposite direction, the alkyne is replacing one solvent molecule after the diene replaces a solvent molecule. When both the alkyne and diene are coordinated a metallacycle transition state is created and the normal Diels-Alder reaction proceeds[14]. (Figure 1.13).

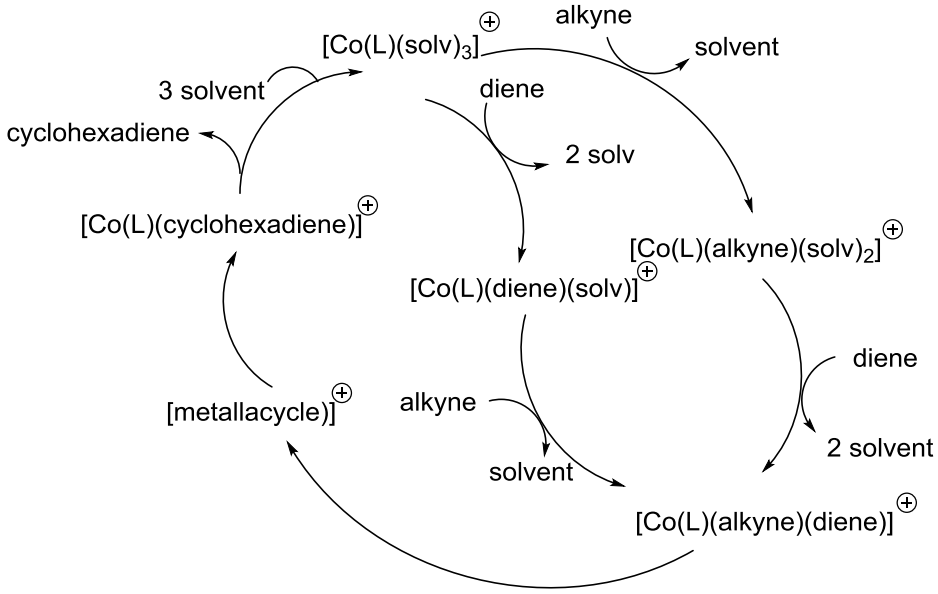


Figure 1.13. Proposed catalytic cycle of the cobalt-catalyzed Diels-Alder reaction[14]. In this scheme L stands for the ligand, solv for solvent.

The outcome is regioselectivity in favor of either the 1,3 or 1,4 product. This depends on the steric effects of the ligand that is being used. The ligand bpy has been reported as a meta-director (1,3) with good regioselectivity and yield. The metallacycle is shown in Figure 1.14. The actual cobalt-catalyzed reaction has four pathways to the desired 1,3-product during the metallacycle where the pathway with the most-favored transition state will be chosen.

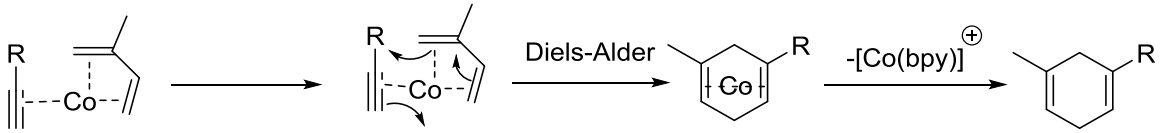
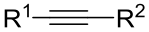


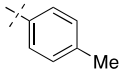
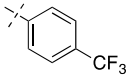
Figure 1.14. Schematically overview of the metallacycle step given with the mechanism[15] of the Diels-Alder reaction.

The substrates (cyclohexadienes) of interest are substituted on the 1-position with phenyl rings, substituted aromatic rings and hetero cycles (see table 1.1 for some examples). On the 3-position of the cyclohexadiene a methyl group will be present from 2-methyl-1,3-butadiene (see figure 1.14).

Also substrates that are 1,2,4-substituted are of interest as it creates a tri substituted olefin and a tetra substituted olefin. Tetra substituted bonds are harder to hydrogenate and are commonly preserved while the tri- substituted bonds will react under iridium catalyzed conditions.

Table 1.1. Substitutions of the acetylene's used in this project.



R^1	R^2	R^1	R^2
H		H	
H		H	
H			
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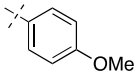
		H	
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In addition to the *meta*-selective Diels-Alder reaction a Lewis-acid catalyzed Diels-alder reaction is also performed. This could be done since there was no line of symmetry in the product which could give rise to meso-compounds. Also a substrate has been prepared through a Birch reduction. Both reactions will be described in: *Results & Discussion*.

The substrates and the hydrogenated products will be completely characterized as is described in the ligand synthesis heading. Furthermore, the chiral substrates will be analyzed with Gas Chromatography (GC) with a MS-detector. Multiple chiral columns will be screened in order to see if the enantiomers can be separated with a good resolution to determine the ee.

2.0 Experimental

2.1 General information

DCM and THF were pre-dried over 4A molecular sieves. THF was freshly distilled over sodium and benzophenon, DCM was freshly distilled over calcium hydride both under nitrogen. TLC-plates were bought at Sigma Aldrich with a diameter of 60Å on aluminium foil. Silica used for purification was bought at VWR-chemicals, 40-63 μM. NMR samples were analysed in $CDCl_3$ at room temperature with a Bruker 400 MHz spectrometer. Zinc iodide was dried under vacuum at 140^0C for 12 hours prior to use. p-Toluenesulfonyl chloride was recrystallized from petroleum ether. Silica was activated by drying for 24 hours at 150° C. Chemicals used for the mobile phase of the preparative-HPLC were bought at VWR and had the analytical grade. All chemicals were commercially bought from Sigma Aldrich, TCI or Apollo unless stated differently. The mass was measured with a Bruker MicroTOF with an ESI source or a Waters GCT Premier with a CI source. IR was measured with a FT-IR apparatus.

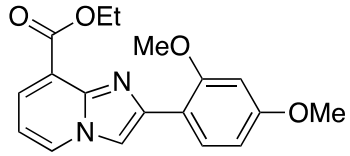
2.2 Ligand synthesis

The ligands have been synthesized according to the reported procedure in the literature[5]. A general procedure is given for each step followed by the exact amounts used for the ligands and the characterization.

General procedure cyclization

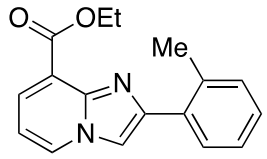
A two-neck flask, equipped with stirrer and condenser, was dried and put under an argon atmosphere. Nicotinic ester and substituted 2-bromo-acetophenon were transferred and dissolved in 2.5 mL 2-butanone/ mmol 2-bromo-acetophenon. The reaction was heated on an oil bath (approximately 85°C) till the reaction was gently refluxing. The reaction was completed after 18 hours (followed by TLC). The precipitate formed in the reaction was filtered off, dissolved in H_2O and quenched with a saturated Na_2CO_3 solution (pH=12). The organic and water layer were separated and the water layer was extracted three times with DCM. The organic layers were combined, washed with a saturated brine solution, and dried over sodium sulphate. The solvent was removed under reduced pressure to obtain the crude product. The product was purified by flash column chromatography.

Entry A:



Ethyl 2-(2,4-dimethoxyphenyl)imidazo[1,2-a]pyridine-8-carboxylate. According to the general procedure the following amounts were used: 1.477 gram (8.9 mmol) of ethyl-2-aminonicotinate, 1.832 gram (7.1 mmol) of 2-bromo-1-(2,4-dimethoxyphenyl)ethan-1-one and 20.0 mL of 2-butanone stirred at 85°C for 18 hours. Flash column chromatography (pentane: ethyl acetate1:1) afforded 1.749 grams (78%) of product as a yellow solid, MP: (154.3 – 158.3^{0}C), R_f =0,1 (Pentane: Ethyl acetate, 5:1). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.47 (d, *J* = 8.5 Hz 1H), 8.23 (dd, *J* = 6.7, 1.4 Hz, 1H), 8.14 (s, 1H), 7.88 (dd, *J* = 7.2 Hz, 1.21 Hz, 1H), 6.74 (t, 1H), 6.64 (dd, *J* = 8.7 Hz, 2.4 Hz, 1H), 6.52 (d, *J* = 2.4, 1H), 4.50 (q, 2H), 3.93 (s, 3H), 3.83 (s, 3H), 1.48 (t, 3H). **^{13}C NMR** ($CDCl_3$, 400 MHz): 164.87, 160.77, 158.04, 142.57, 141.69, 130.36, 129.30, 128.69, 119.14, 115.28, 111.67, 110.56, 104.97, 98.46, 61.51, 55.46, 55.44, 14.43. **IR** (NaCl, neat, cm^{-1}): *v* = 2982.99, 2838.95, 2725.06, 1611.26, 1579.45, 1491.19, 1357.55, 1293.64, 1209.83,
HRMS-ESI m/z: $[M+H]^+$ Calc. for $C_{18}H_{18}N_2O_4H$ 327.1339; Found 327.1346.

Entry E

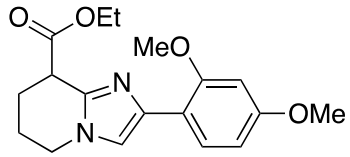


Ethyl2-(o-tolyl)imidazo[1,2-a]pyridine-8-carboxylate. According to the general procedure the following amounts were used: 744 mg (4.5 mmol) of ethyl-2-aminonicotinate, 0.66 mL (4.5 mmol) of 2-bromo-1-(*o*-tolyl)ethan-1-one and 11.25 mL of 2-butanone stirred at 85°C for 35 hours. Flash column chromatography (100% DCM) afforded 488 mg (46%) of product as yellow oil, R_f = 0.54 (EtOAc: Pentane, 1:1). **^{1}H NMR** ($CDCl_3$, 400 MHz δ 8.30 (dd, J = 6.7, 1.3 Hz, 1H), 8.00 – 7.95 (m, 1H), 7.92 (dd, J = 7.2, 1.3 Hz, 1H), 7.76 (s, 1H), 7.31 – 7.22 (m, 3H), 6.83 – 6.77 (m, 1H), 4.51 (q, J = 7.1 Hz, 2H), 2.58 (s, 3H), 1.48 (t, J = 7.1 Hz, 3H).. **^{13}C NMR** ($CDCl_3$, 400 MHz): 164.71, 146.55, 141.93, 136.02, 132.96, 130.86, 129.90, 129.35, 128.77, 127.90, 125.91, 119.90, 111.13, 110.99, 61.51, 21.67, 14.34.
IR (NaCl, neat, cm^{-1}): *v* = 3067, 2981, 2933, 1724, 1548, 1496, 1465, 1361, 1284, 1265, 1186, 1144, 1040, 756. **HRMS-ESI** m/z: $[M+H]^+$ Calc. for $C_{17}H_{18}N_2O_2H$ 303.1104; Found 303.1111.

General procedure pyridine-ring reduction

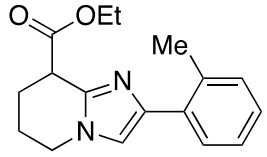
A beaker glass was equipped with a stirrer. **A/E** was transferred and dissolved in 2,2,2-trifluoroacetic acid. Palladium on carbon was added and the top of the beaker glass was sealed with punctured aluminium foil. The hydrogenation was set up for 18 hours on 100 bar hydrogen gas pressure to completion. The palladium on carbon was filtered of on Celite and washed with DCM. A saturated Na_2CO_3 solution was added (pH= >8), the layers were separated and the water layer was extracted three times with DCM. The organic layers were combined, washed with a saturated brine solution and dried over sodium sulphate. The solvent was removed under reduced pressure to obtain the product. The product could be used without any further purification.

Entry B:



Ethyl-2-(2,4-dimethoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-8-carboxylate, According to the general procedure the following amounts were used: , 2.011 grams (6.2 mmol) of **A**, 244 mg (2.3 mmol) of palladium on carbon and 10 mL of 2,2,2-trifluoroacetic acid. The product was obtained yellow/brownish solid, MP: (112.6-119.8^{0}C), in 1.60 gram (79%) yield, R_f =0,44 (ethylacetate). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.05 (d, J = 8.6Hz, 1H), 7.30 (s, 1H), 6.55 (dd, J = 8.6 Hz, 2.5 Hz, 1H), 6.50 (d, J = 2.4 Hz, 1H), 4.28-4.15 (m, 2H), 4.10-4.00 (m, 2H), 3.98-3.91 (m, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 2.33-2.25 (m, 1H), 2.24-2.08 (m, 2H), 2.01-1.92 (m, 2H), 1.29 (t, 3H). **^{13}C NMR** ($CDCl_3$, 400 MHz): 171.51, 158.66, 156.25, 139.65, 135.95, 127.70, 116.75, 115.77, 103.91, 97.83, 60.63, 54.76, 54.67, 43.87, 40.67, 24.61, 19.91, 13.60. **IR** (NaCl, neat, cm^{-1}): v= 2940.19, 2869.41, 2051.02, 1716.64, 1614.44, 1582.97, 1464.74, 1289.79, **HRMS-ESI** m/z: $[M+H]^+$ Calc. for $C_{18}H_{22}O_4N_2H$; 331.1652; Found 331,1663.

Entry F:

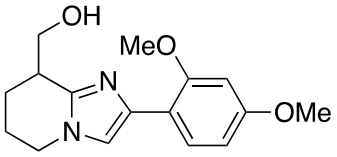


Ethyl 2-(*o*-tolyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-8-carboxylate. According to the general procedure the following amounts have been used: 0.5 gram (1.8 mmol) of **E**, 61 mg (0.6 mmol) of palladium on carbon and 5 mL of 2,2,2-trifluoroacetic acid. The product was obtained as brown oil in 404 mg (81%) yield, R_f =0,70 (100% Ethylacetate). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.75 (m, 1H), 7.23-7,13 (m, 3H), 6.94 (s, 1H), 4.29-4.16 (m, 2H), 4.15-4.04 (m, 2H), 4.03-3.94 (m, 1H), 2.46 (s, 3H), 2.37-2.28 (m, 1H), 2.26-2.13 (m, 2H), 2.06-1.96 (m, 1H), 1.29 (t, 3H). **^{13}C NMR** ($CDCl_3$, 400 MHz): 172.10, 140.73, 140.42, 134.89, 133.73, 130.52, 128.62, 126.58, 125.72, 116.92, 77.48, 77.16, 76.84, 61.32, 44.56, 41.25, 25.08, 21.62, 20.51, 14.17, 14.06. **IR** (NaCl, neat, cm^{-1}): v= 3348.71, 3145.11, 3059.97, 2959.01, 2871.63, 1921.37, 1704.55, 1694.57, 1505.63, 1480.48, 1463.44, 1379.52, 1286.03, 1253.45, 1137.78, 1094.93, 1029.26, 948.10. **HRMS-ESI** m/z: $[M+H]^+$ Calc. for $C_{17}H_{21}O_2N_2H$; 285.1595 ; Found 285,1607.

General procedure ester reduction,

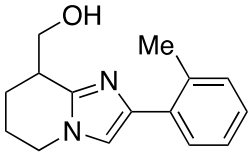
A three-neck round bottom flask, equipped with stirrer and condenser, was dred and put under an argon atmosphere. The flask was put in a ice-bath to cool the temperature down (~0°C). A slurry was made of $LiAlH_4$ and THF. **B** or **F** was dissolved in THF and added slowly through a syringe. After 10 minutes the ice-bath was removed and the mixture was stirred for 18 hours. After completion (followed by TLC) n mL H_2O was added, 2n mL 2.0 M NaOH solution (were n is the amount in mol of $LiAlH_4$). The reaction was stirred for 30 minutes and an additional n mL H_2O was added. The precipitate was filtered off through Celite and washed with THF. The product was obtained by removing the solvent of the filtrate and purification by flash chromatography (100% ethyl acetate).

Entry C:

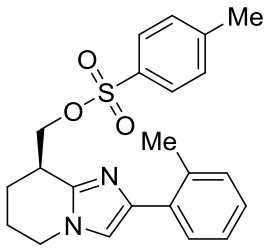


(2-(2,4-dimethoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-8-yl)methanol. According to the general procedure the following amounts have been used: 317.92 mg (0.96 mmol) of **B** in 2.5 mL of THF, 110.51 mg (2.91 mmol) of $LiAlH_4$ in 2.5 mL of THF stirred at room temperature for 18 hours. 147 mg (54%) of **C** was obtained after purification as a yellow solid, MP: (159.8 – 163.8^{0}C), R_f =0,36 (Ethylacetate). 20 mg of **C** was dissolved in 0.75 mL of absolute ethanol and 0.75 mL of isopropanol. The enantiomers were separated at 20 bar pressure with hexane: isopropanol, 50:50 on a Chiracel OD-column (20x250 mm). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.04 (d, J = 7.5 Hz, 1H), 7.28 (s, 1H), 6.57 (dd, J = 8.7 Hz, 2.5 Hz, 1H), 6.51 (d, J = 2.3 Hz, 1H), 5.51 (bs, 1H), 4.09-4.00 (m, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 3.70 (t, 1H), 3.15-3.05 (h, J = 14.66 Hz, 5.2 Hz, 1H), 2.16-1.92 (m, 3H), 1.51-1.38 (m, 1H), 1.29-1.17 (m, 2H). **^{13}C NMR** ($CDCl_3$, 400 MHz): 159.56, 157.00, 146.80, 135.80, 128.18, 116.69, 115.89, 104.74, 98.68, 66.10, 55.55, 55.43, 44.51, 37.22, 29.84, 23.75, 22.44. **IR** (NaCl, neat, cm^{-1}): ν= 3349.93, 2998.13, 2941.91, 2837.07, 1673.86, 1614.69, 1583.01, 1557.09, 1482.65, 1436.76, 1376.35, 1290.69, 1208.37, 1035.42. **HRMS** m/z: $[M+H]^+$ Calc. for $C_{16}H_{20}O_3N_2H$ 289.1547; Found 289,1560. **Specific rotation**: $[\alpha]^{25}_D$ ($CHCl_3$: 0.230 g.100 ml^{-1})= 53.478

Entry G:

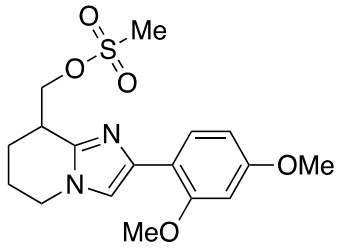


(2-(o-tolyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-8-yl)methanol. According to the general procedure the following amount were used: 295 mg (mmol) of **F** in 0.5 mL of THF, 81.87 mg (mmol) of $LiAlH_4$ in 2.0 mL of THF stirred at room temperature for 18 hours. 129 mg (51%) of **G** was obtained after purification as a brown solid, R_f = 0.26 (ethylacetate). 50 mg of **G** was dissolved in 1.5 mL of isopropanol. The enantiomers were separated at 20 bar pressure with hexane: isopropanol, 50:50. **^{1}H NMR** (CDCl3, 400 MHz): δ 7.81 (dd, J = 7.6 Hz, 1.4 Hz, 1H), 7.25-7.14 (m, 3H), 6.96 (s, 1H), 5.59 (bs, 1H), 4.09 (m, 1H), 3.95-3.86 (td, J = 11.9, 4,0 Hz, 1H), 3.86-3.78 (dd, J= 10.7 Hz, 4.6Hz, 1H), 3.7 (t, 1H), 3.11 (sep, J = 5.2 Hz, 1H), 2.48 (s, 3H), 2.20-2.11 (m, 1H), 2.08-1.95 (m, 2H), 1.46(dq, J = 20.0 Hz, 2.1 Hz, 1H). **^{13}C NMR** (CDCl3, 400 MHz): δ 172.10, 140.73, 140.42, 134.89, 133.73, 130.52, 128.62, 126.58, 125.72, 116.92, 77.48, 77.16, 76.84, 61.32, 44.56, 41.25, 25.08, 21.62, 20.51, 14.17, 14.06. **IR** (NaCl, neat, cm-1): ν= 3359.84, 3054.69, 2949.85, 2865.65, 1667.77, 1603.76, 1511.44, 1442.45, 1378.96, 1202.97, 1089.85, 1059.27. **HRMS** m/z: [M+H]+ Calc. for 243.1492 ; Found 243.1491. **Specific rotation**: $[\propto]^{25}_D$ ($CHCl_3$, c = 0.214) =65.421.

Entry H: 

(R)-(2-(o-tolyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-8-yl)methyl 4-methylbenzenesulfonate. ***Procedure for the tosylation:*** A two-neck round bottom flask, equipped with stirrer, was dried and put under an argon atmosphere. 100 mg (0.4 mmol) of **G**, 1.4 mL of pyridine and 1.4 mL of DCM were added. The reaction was cooled to ~0°C on an ice-bath and 241 mg (1.3 mmol) of p-toluenesulfonyl chloride was added in 1.4 mL of DCM. The reaction was allowed to reach room temperature and was stirred for 17 hours. After the reaction went to completion (followed by TLC) the reaction was quenched with 3 mL (10%) Na_2CO_3 solution. The layers were separated, the water layer was extracted three times with DCM, and the organic phases were combined and washed with saturated brine solution. The organic phase was dried over sodium sulphate and the solvent was removed. The product was purified by flash column chromatography (DCM:MeOH, 40:1) to obtain 96 mg (70%) of **H** as a white foam, R_f= 0.25 (DCM:MeOH, 40:1). 1H NMR (CDCl3, 400 MHz): δ 7.76 (d, *J* = 8 Hz, 2H), 7.67-7.65 (m, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.23-7.11 (m, 3H), 6.89 (s, 1H), 4.61 (dd, *J* = 9.6, 3.8 Hz, 1H), 4.27 (t, *J* = 12 Hz, 1H), 4.10-3.89 (m, 2H), 3.33-3.26 (m, 1H), 2.41 (s, 3H), 2.40 (s, 3H), 2.28-2.18 (m, 1H), 2.18-2.09 (m, 1H), 2.01-1.80 (m, 2H). 13C NMR (CDCl3, 100 MHz,): δ. 144.91, 142.41, 140.28, 134.85, 133.65, 132.77, 130.76, 129.97, 128.46, 128.11, 126.74, 125.92, 117.14, 71.73, 44.83, 35.06, 24.27, 21.84, 21.73, 21.41. **IR** (NaCl, neat, cm-1): *v* = 2953, 2922, 1598, 1448, 1359, 1189, 1176, 1121, 1097, 1043, 953, 833, 811, 742. **Specific rotation**: $[\propto]^{25}_{D}$ (CHCl3, c = 0.4698)= 17.021. **HRMS (EI)** m/z: $[M+H]^+$ Calc. for $C_{22}H_{25}N_2O_3S$ = 397.1580 Found 397.1581.

Entry D:



(R)-(2-(2,4-dimethoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-8-yl)methyl methanesulfonate. ***Procedure for the mesylation:***
A two-neck round bottom flask, equipped with stirrer, was dried and put under an argon atmosphere. 31 mg (0.69 mmol) of NaH was added in 5mL THF at 0°C, cooled on an ice-bath. 147 mg (0.65 mmol) of **LC_1** was added and the mixture was stirred for 20 minutes at room temperature. 79 mg (0.69 mmol) of methylsulfonyl chloride was added at 0°C and the reaction was stirred for 10 minutes. The reaction was allowed to reach room temperature and was stirred for 17 hours. The reaction was quenched with Na_2CO_3 solution. The layers were separated, the water layer was extracted three times with DCM, the organic phases were combined and washed with saturated brine solution. The combined organic phase was dried over sodium sulphate and solvent was removed. The product was purified by flash column chromatography (DCM: EtOAc, 40:1) to obtain D as white foam in 88% yield, Rf=0.06 (DCM: EtOAc, 40:1).**^{1}H NMR** (CDCl3, 400 MHz): δ 8.00 (d, *J* = 12.0 Hz, 1H), 7.29 (s, 1H), 6.56 (dd, *J*= 8.6, 2.4, 1H), 6.51 (d, *J* = 2.3 Hz, 1H), 4.64-4.73 (m, 2H), 4.04-4.00 (m, 1H), 3.98-3.91 (m, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 3.36-3.30 (m, 1H), 2.99 (s, 3H), 2.23-2.12 (m, 2H), 2.01-1.86 (m, 3H). 13C NMR (CDCl3, 100 MHz,): δ 159.52, 157.01, 142.18, 136.36, 127.82, 117.68, 116.24, 104.79, 98.68, 71.82, 55.52, 55.41, 44.77, 37.14, 35.45,24.31, 21.77. **IR** (NaCl, neat, cm-1): *ν* = 2926, 1613, 1580, 1552, 1511, 1481, 1458, 1438, 1413, 1348, 1288, 1208, 1174, 1069, 1032, 950, 901, 832. **Specific rotation**: $[\propto]^{25}_{D}$ (CHCl3, c = 0.1897) = 75.263. **HRMS (EI)** m/z: $[M+H]^+$ Calc. for $C_{17}H_{23}N_2O_5S$ = 367.1322; Found 367.1328.

2.3 *meta*-selective Diels-Alder reaction

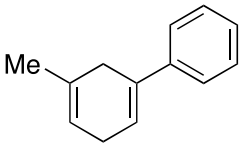
Procedure for the complexation of $CoBr_2$(bpy):
A dry 10 mL two-neck round bottom flask, equipped with stirrer, was put under argon. 0.446 gram (2.04 mmol) of dry $CoBr_2$ was added and dissolved in 4.0 mL THF. A solution of 0.323 gram (2.07 mmol) 2,2-bipyridyl in 4.0 mL dry THF was added slowly through a syringe. The reaction was stirred for 17 hours at room temperature. The solvent was filtered off and the blue precipitate was washed with a small amount of THF. The precipitate was dried under vacuum for 8 hours to obtain the air-stable complex as a blue solid (99%).

General procedure for the cobalt-catalysed Diels-Alder reaction[13]:
In a dried vial, equipped with stirring bar and under argon atmosphere, $CoBr_2$(bpy) (5 mol%), zinc iodide (10 mol%), iron powder (10 mol%) and zinc powder (10 mol%), were transferred and DCM was added (0.5 ml/mmol acetylene).The mixture was heated to boiling point till the colour of the reaction turned grey-green. The mixture was cooled to room temperature and the acetylene of and 2-methyl-1,3-butadiene were added. The vial was capped and stirred at room temperature for 24 hours. After completion of the reaction 1.0 mL of pentane was added and filtered through silica with pentane. The solvent was removed under reduced pressure to obtain the crude product. The reaction was purified by flash chromatography with activated silica (pentane 100%).

General procedure for the deprotection of trimethylsilyl acetylenes:

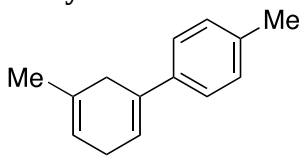
In a 4 mL vial, equipped with stirrer, 1.5 mL of a H_2O: MeOH (1:2) solution and 149 mg (2.42 mmol) of KOH were added. The acetylene of choice was added (2.42 mmol) and the vial was capped. After 8 hours the reaction was quenched with 2.0 mL of H_2O and 5.0 mL of DCM was added. The layers were separated and the water layer was extracted three times with DCM. The combined organic layers were dried over sodium sulphate and the solvent was removed under reduced pressure in an ice-bath. The acetylene could be used without further purification[16].

Entry 1:



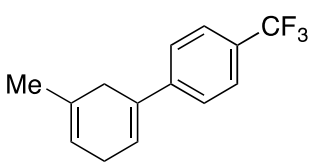
3-methyl-2,5-dihydro-1,1'-biphenyl, According to the general procedure, the following amounts were used: phenylacetylene (632 mg, 6.2 mmol), 2-methyl-1,3-butadiene (545 mg, 8.0 mmol), $CoBr_2$(bpy) (117 mg, 0.312 mmol), ZnI_2 (216 mg, 0.68 mmol), Fe (34 mg, 0.60 mmol), Zn (40 mg, 0.62 mmol), dichloromethane (3.0 mL). After column chromatography, **1** was obtained as colourless oil. 73% yield. R_f = 0.58 (pentane), **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.44 (m, 2H), 7.34 (m, 2H), 7.25 (m, 1H), 6.14 (s, 1H), 5.50 (s, 1H), 2.94 (m, 4H), 1.79 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 141.65, 141.50, 138.46, 133.91, 131.48, 128.82, 128.79, 128.40, 128.13, 127.32, 127.29, 126.99, 126.74, 125.12, 124.41, 121.77, 118.06, 34.28, 33.03, 32.29, 29.87, 29.09, 28.45, 23.51, 23.06, 22.50, 21.69, 14.22. **IR** (NaCl, CCl_4, cm^{-1}): ν =: 3080.66, 3057.15, 2923.81, 2850.91, 2728.27, 1944.04, 1600.80, 1494.26, 1445.48, 1384.33, 1267.34, 962.63 cm^{-1}. **HRMS-CI:** m/z: $[M]^+$ Calc. for $C_{13}H_{14}$ 170.1096; Found 170.1074.

Entry 2:



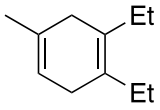
3,4'-dimethyl-2,5-dihydro-1,1'-biphenyl. According to the general procedure, the following amounts were used: 1-ethynyl-4-methylbenzene (696 mg, 6.0 mmol), 2-methyl-1,3-butadiene (613 mg, 9.0 mmol), $CoBr_2$(bpy) (104 mg, 0.28 mmol), ZnI_2 (214 mg, 0.67 mmol), Fe (39 mg, 0.70 mmol), Zn (32 mg, 0.49 mmol), dichloromethane (3.0 mL). After column chromatography, **2** was obtained as a colourless oil. 76% yield. R_f = 0.32 (pentane). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.33 (d, 2H), 7.14 (d, 2H), 6.09 (m, 1H), 5.48 (m, 1H), 2.91 (m, 4H), 2.34 (s, 3H), 1.77 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 138.80, 136.65, 133.68, 131.51, 129.09, 124.97, 120.91, 118.10, 33.06, 28.42, 23.53, 21.21. **IR** (NaCl, CCl_4, cm^{-1}): ν = 3027.67, 3050.61, 2984.41, 2926.56, 2819.59, 2730.78, 2684.96, 2305.67, 1904.03, 1550.06, 1512.94, 1446.80, 1424.22, 1384.76, 1219.55, 979.81, 895.79. **HRMS-CI:** m/z: $[M]^+$ Calc. for $C_{14}H_{16}$ 184.1252; Found 184.1254.

Entry 3:



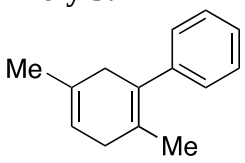
3-methyl-4'-(trifluoromethyl)-2,5-dihydro-1,1'-biphenyl. According to the general procedure, the following amounts were used: 4-ethynyl-α,α,α-trifluorotoluene (1.022 g, 6.0 mmol), 2-methyl-1,3-butadiene (613 mg, 9.0 mmol), $CoBr_2$(bpy) (111 mg, 0.30 mmol), ZnI_2 (221mg, 0.69 mmol), Fe (41 mg, 0.56 mmol), Zn (31 mg, 0.63 mmol), dichloromethane (3.0 mL). After column chromatography, **3** was obtained as a white solid (mp: 41.6 – 44.2 ^{0}C). 65% yield, R_f = 0.83(pentane), **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.55 (dd, 4H) 6.23 (m, 1H), 5.50 (m, 1H), 2.94 (m, 4H), 1.79 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 145.06, 145.04, 133.00, 131.20, 128.77, 125.41, 125.37, 125.34, 125.31, 124.05, 117.96, 32.84, 28.47, 23.46. **IR** (NaCl, CCl_4, cm^{-1}): ν = 3007.70, 3031.62, 2969.57, 2908.96, 2879.51, 2855.83, 2819.89, 2684.60, 2305.07, 1919.19, 1739.08, 1646.90, 1617.88, 1574.62, 1549.93, 1438.37, 1426.08, 1326.41, 1264.11, 1216.88, 1168.64, 1130.12, 1070.87, 1016.87, 939.01, 853.88. **HRMS-CI:** m/z: $[M]^+$ Calc. for $C_{14}H_{13}F_3$ 238.0969; Found 238.0983.

Entry 4:



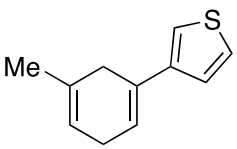
1,2-diethyl-4-methylcyclohexa-1,4-diene. According to the general procedure, the following amounts were used: 3-hexyne (493 mg, 6.0 mmol), 2-methyl-1,3-butadiene (613 mg, 9.0 mmol), CoBr2(bpy) (114 mg, 0.30 mmol), ZnI2 (214mg, 0.67 mmol), Fe (39 mg, 0.70 mmol), Zn (34 mg, 0.52 mmol), dichloromethane (3.0 mL). After column chromatography, the product was obtained as a colorless oil, 60% yield. R*f* =0,80 (Pentane). **^{1}H NMR** (CDCl3, 400 MHz): δ 5.43-5.39 (m, 1H), 2.68-2.50 (m, 4H), 2.10-2.01 (m, 4H), 1.68 (m, 3H), 1.03-0.93 (td, J=7.61, 7.58, 6.78, 6H). **^{13}C NMR** (CDCl3, 100 MHz): 130.72, 127.75, 118.04, 34.14, 30.31, 24.46, 24.28, 22.09, 12.33, 12.19. **IR** (NaCl, neat, cm-1): ν = 3051.06, 2966.02, 2813.32, 1539.92, 1264.78, 1034.54. **HRMS-CI** m/z: $[M+H]^+$ Calc. for $C_{11}H_{19}$ 151.1487; Found 151.1489.

Entry 5:



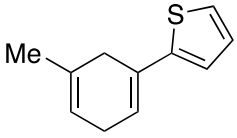
3,6-dimethyl-2,5-dihydro-1,1'-biphenyl. According to the general procedure, the following amounts were used: 1-phenyl-1-propyne (371 mg, 3.0 mmol), 2-methyl-1,3-butadiene (409 mg, 6.0 mmol), $CoBr_2$(bpy) (40 mg, 0.11 mmol), ZnI_2 (71 mg, 0.22 mmol), Fe (14 mg, 0.25 mmol), Zn (13 mg, 0.20 mmol), dichloromethane (1.5 mL). After column chromatography, **5** was obtained as colourless oil. 61% yield, R_f = 0.37 (pentane), **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.33 (m, 2H), 7.23(m, 1H), 7.18 (m, 2H), 5.47(s, 1H), 2.80 (m, 4H), 1.71 (s, 3H), 1.59(s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 143.19, 131.63, 129.45, 128.13, 128.10, 127.92, 127.89, 127.83, 126.23, 126.20, 125.98, 125.96, 118.85, 118.32, 37.66, 33.81, 22.66, 19.59. **IR** (NaCl, neat, cm^{-1}): ν =: 3075.27, 3055.93, 2964.48, 2924.95, 2815.68, 2727.39, 1945.65, 1806.71, 1774.21, 1666.59, 1600.86, 1574.69, 1489.89, 1441.35, 1377.01 1265.49, 1069.92, 918.51, 785.52, 763.00, 700.37. **HRMS-CI**: m/z: [M]+ Calc. for $C_{14}H_{16}$ 184.1252; Found 184.1258.

Entry 6:



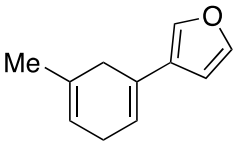
3-(5-methylcyclohexa-1,4-dien-1-yl)thiophene. According to the general procedure, the following amounts were used: 3-ethynyl-thiophene (659 mg, 6.1 mmol), 2-methyl-1,3-butadiene (613 mg, 9.0 mmol), $CoBr_2$(bpy) (107 mg, 0.29 mmol), ZnI_2 (207 mg, 0.65 mmol), Fe (39 mg, 0.70 mmol), Zn (32 mg, 0.49 mmol), dichloromethane (3.0 mL). After column chromatography, **6** was obtained as a white solid, (MP: 46.8 - 51.8 °C). 18% yield, R_f = 0.51 (pentane), **^{1}H NMR** (CDCL3. 400 MHz): δ 7.30 (m, 2H), 7.14 (S, 1H), 6.20 (s, 1H), 5.51 (s, 1H), 2.93 (m, 4H), 1.81 (s, 3H). **^{13}C NMR** (CDCL3, 400 MHz): 143.15, 131.14, 129.25, 125.38, 124.77, 120.75, 118.38, 118.11, 77.48, 77.16, 76.84, 32.97, 27.98, 23.47.
IR (NaCl, CCl_4, cm^{-1}): v=: 2324.22, 2817.01, 2676.24, 1751.01, 1696.25, 1554.18, 1445.93, 1380.94, 1406.45, 1334.20, 1249.82, 1150.92, 962.21 cm^{-}1. **HRMS-CI:** m/z: $[M]^+$ Calc. for $C_{11}H_{12}S$ 179.0660; Found 176.0666.

Entry 7:



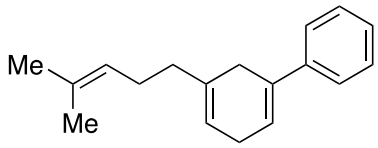
2-(5-methylcyclohexa-1,4-dien-1-yl)thiophene, According to the general procedure, the following amounts were used: (thiophen-2-ylethynyl)trimethylsilane, deprotected according to the general procedure (219 mg, KOH, 2.25 mL of MeOH:H_2O), 2-methyl-1,3-butadiene (170 mg, 2.5 mmol), $CoBr_2$(bpy) (40 mg, 0.12 mmol), ZnI_2 (69 mg, 0.20 mmol), Fe (10 mg, 0.20 mmol), Zn (14 mg, 0.20 mmol), dichloromethane (1.5 mL). After column chromatography, **7** was obtained as a colourless oil, 22% yield, R_f = 0.43 (pentane). **^{1}H NMR** ($CDCl_3$. 400 MHz): δ 7.15-7.10 (m, 2H), 6.98 (d, J= 3.40, 2H), 6.19 (m, 1H), 5.48 (m, 1H), 3.00-2.81 (m, 4H), 1.76 (m, 3H). **^{13}C NMR** ($CDCl_3$, 400 MHz): δ. 146.05, 130.82, 128.39, 127.13, 124.63, 122.86, 121.37, 120.74, 117.93, 33.02, 27.86, 23.28.

Entry 8:



3-(5-methylcyclohexa-1,4-dien-1-yl)furan. According to the general procedure, the following amounts were used: (furan-3-ylethynyl)trimethylsilane, deprotected according to the general procedure (188 mg, KOH, 1.90 mL of MeOH:H_2O), 2-methyl-1,3-butadiene (170 mg, 2.5 mmol), $CoBr_2$(bpy) (41 mg, 0.12 mmol), ZnI_2 (68 mg, 0.20 mmol), Fe (11 mg, 0.20 mmol), Zn (13 mg, 0.20 mmol), dichloromethane (1.5 mL). After column chromatography, **8** was obtained as a colourless oil, 18% yield, R_f = 0.25 (pentane). **^{1}H NMR** ($CDCl_3$. 400 MHz): δ 7.42-4.39 (m, 1H), 7.39-7.35 (m, 1H), 6.59 (dd, J= 2.0, 0.9 Hz, 1H), 6.04-5.98 (m, 1H), 5.45-5.45 (m, 1H), 2.91-2.75 (m, 4H), 1.81-1.74 (m, 3H). **^{13}C NMR** ($CDCl_3$, 400 MHz): δ 143.11, 137.59, 130.80, 127.17, 125.70, 119.57, 118.15, 107.17, 32.29, 27.53, 23.30.

Entry 12:



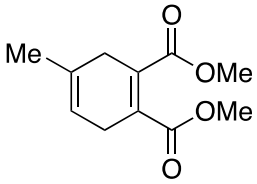
3-(4-methylpent-3-en-1-yl)-2,5-dihydro-1,1'-biphenyl. According to the general procedure, the following amounts were used: myrcene (0.4 mL, 2.3 mmol), 2-methyl-1,3-butadiene (170 mg, 2.5 mmol), $CoBr_2$(bpy) (39 mg, 0.12 mmol), ZnI_2 (64 mg, 0.20 mmol), Fe (11 mg, 0.20 mmol), Zn (13 mg, 0.20 mmol), dichloromethane (3.0 mL). After column chromatography, **12** was obtained as a colourless oil. 86% yield, R_f = 0.30 (pentane). **^{1}H NMR** ($CDCl_3$. 400 MHz): δ 7.45-7.30 (m, 5H), 6.14-6.11 (m, 1H), 5.45-5.39 (m, 1H), 5.15 (ddt, J= 7.0, 5.6, 1.4 Hz, 1H), 3.04-2.87 (m, 4H), 2.21-2.04 (m, 4H), 1.70 (d, J= 1.4, 3H), 1.63 (d, J= 1.3 Hz, 3H).

Note: *The exact experimental in weights of unsuccessful substrates will not be written down. The general procedure was followed leading to no product.*

2.4 Procedure Lewis-Acid Catalysed Diels-Alder

A vial, equipped with stirrer, was dried and put under inert argon atmosphere. 3.8 mL (mmol) of 2-methyl-1,3-butadiene, 0.83 mL (mmol)of were added and dissolved in 30 mL DCM. The reaction was stirred cooled to 0°C and 473 mg (mmol) of aluminium chloride was added. The reaction was allowed to reach room temperature and was stirred for 18 hours. When the reaction went to completion (followed by TLC) H_2O was added to quench the reaction. The layers were separated and the water layer was extracted three times with DCM. The combined organic layers were washed with a saturated brine solution, dried over sodium sulphate and the solvent was removed under reduced pressure. The product was purified by flash column chromatography (pentane: ethyl acetate, 20:1).

Entry 13:

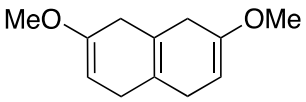


dimethyl-4-methylcyclohexa-1,4-diene-1,2-dicarboxylate, colourless oil, 50 % yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.70 (bs, 3H), 2.84 – 2.92 (m, 2H), 2.95 – 3.04 (m, 2H), 3.77 (d, 2.47 Hz, 6H), 5.93 (m, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 22.68, 28.71, 32.18, 52.30, 77.16, 116.69, 128.43, 129.80, 132.39, 132.98, 168.50, 168.74. The product is reported[17] and needs no further characterization.

2.5 Procedure Birch Reduction

A 500 mL three-neck round bottom flask, equipped with stirrer and a dry-ice condenser, was dried and put under argon atmosphere. 1.051 gram (5.6 mmol) of 2,7-dimethoxynaphtalene was added in 16.7 mL of absolute ethanol and 100 mL of diethyl ether. The condenser and reaction flask were cooled down to -78°C, dry-ice/acetone, and 250 mL of ammonia was slowly added from an ammonia cylinder. The reaction was allowed to reach room temperature and 1.046 gram (203 mmol) of lithium wire was added slowly in 1.5 hour. Halfway of the lithium addition, 20 mL of absolute ethanol was added. After the blue colour completely disappeared ammoniumchloride was added to neutralize the reaction with diethyl ether and 150 mL H_2O. The ammonia was allowed to evaporate from the reaction. Afterwards the water layer and organic layer were separated, the water layer was extracted three times with diethyl ether and the combined layers were washed with brine. The reaction was dried over sodium sulphate and the solvent was removed. The crude product required no further purification prior to use[18].

Entry 14:



2,7-dimethoxy-1,4,5,8-tetrahydronaphthalene, 52% yield, white solid, **^{1}H NMR** ($CDCl_3$. 400 MHz): δ 4.64 (t, J= 3.4 Hz, 2H), 3.56 (s, 6H), 2.74-2.58 (m, 8H). The product is reported[18] and needs no further characterization.

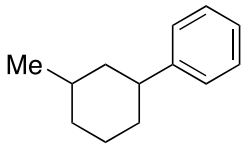
2.6 General Hydrogenation Procedure

General procedure for hydrogenation[4]

A 4.0 mL vial, equipped with stirrer, is dried and put under nitrogen. The appropriate amount of catalyst in loaded in the vial followed by a solution of the substrate in the appropriate solvent. The vial is closed with punctured aluminium foil and is placed in the reactor with three other vials to restrict the movement in the reactor. The reactor is flushed with at least 7 bar of argon for three times followed by three times hydrogen gas. The reactor is filled with the wanted pressure of hydrogen gas, the stirrer is turned on, and if required, the heather. After the hydrogenation is completed the pressure in the reactor is reduced to atmospheric pressure. The solvent in the samples is removed with reduced pressure. A solution of pentane: diethyl ether (1:1) is pushed through a pipet filled with a piece of cotton and at least two fingers of silica (Celite in case of palladium on carbon) to create an appropriate gel. The pentane: diethyl ether solution is used to load the remaining's of the vial on the gel and to elute the compound without the catalyst. After removal of the solvent under reduced pressure, the sample can be analysed.

2.7 Experimental hydrogenation data

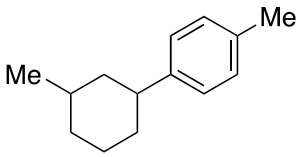
Entry 15:



(3-methylcyclohexyl)benzene. According to the general procedure, the following amounts were used: 0.55 mol % catalyst with (**R**)-ligand **V**, 10 mg of substrate, 17 hours at room temperature under 50 bar hydrogen pressure in 0.5 mL of DCM. The product was obtained as colourless oil in 91% yield with 100% conversion, R_f = 0.29 (pentane). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.36-7.21 (m, 4H), 7.21-7.14 (m, 1H), 2.81 9m, 1H), 2.05 (m, 1H), 1.89-1.71 (m, 2H), 1.67-1.39 (m, 6H), 1.06 (d, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 147.65, 128.68, 128.22, 127.98, 127.17, 127.15, 127.02, 125.63, 77.33, 77.21, 77.01, 76.69, 39.89, 37.86, 33.90, 31.96, 27.93, 21.14, 18.74. **IR** (NaCl, CCl_4, cm^{-1}): ν =: 3584.01, 3063.88, 3028.79, 2958.61, 2945.44, 2851.77, 1601.65, 1583.79, 1493.13, 1459.90, 1378.26, 1260.56, 1157.33, 1072.20, 1025.88. **HRMS-CI:** m/z: $[M]^+$ Calc. for $C_{13}H_{18}$; 175.1487; Found 175.1499. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ ($CDCl_3$, 0.163 $g.mL^{-1}$)= -1.22.

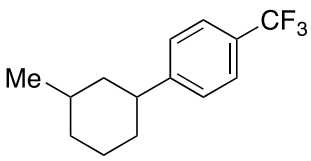
The enantiomers were separated with GC-MS with an Astec® Chiraldex-β-DM column (30m, 0.25 mm, d_f 0.12 μM), split ratio: 50, helium flow: 1 $mL.min^{-1}$, 80°C isothermal for 250 min. Peaks: 145 (cis), 149 (cis), 191 (trans, minor) and 199 (trans, major) minutes.

Entry 16:



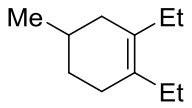
1-methyl-4-(3-methylcyclohexyl)benzene. According to the general procedure, the following amounts were used: 0.53 mol % catalyst with (**R**)-ligand **V**, 11 mg of substrate, 17 hours at room temperature under 50 bar hydrogen pressure in 0.5 mL of DCM. The product was obtained as colourless oil in 81% yield with 100% conversion, R_f = 0.24 (pentane). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.12 (m, 4H), 2.77 (m, 1H), 2.32 (s, 3H), 2.04 (m, 1H), 1.78-1.69 (m, 2H), 1.64.1.39 (m, 6H), 1.05 (d, 3H) . **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 144.81, 135.19, 129.11, 129.07, 127.04, 40.14, 37.56, 34.13, 32.14, 29.86, 28.09, 21.32, 21.10, 18.92. **IR** (NaCl, CCl_4, cm^{-1}): ν =: 2925.01, 2852.84, 1560.04, 1545.88, 1459.84, 1377.79, 1256.76, 1006.25 **HRMS-CI:** m/z: $[M]^+$ Calc. for $C_{14}H_{20}$; 188.1565 ; Found 188.1575. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$ ($CDCl_3$, 0.103 $g.mL^{-1}$)= 1.94.
The enantiomers were separated with GC-MS with an Astec® Chiraldex-β-DM column (30m, 0.25 mm, d_f 0.12 μM), split ratio: 50, helium flow: 1 $mL.min^{-1}$, 80°C isothermal for 300 min. Peaks: 208 (cis), 215 (cis), 265 (trans, minor) and 275 (trans, major) minutes.

Entry 17:



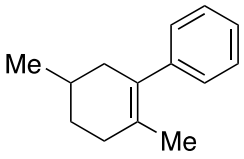
1-(3-methylcyclohexyl)-4-(trifluoromethyl)benzene.
According to the general procedure, the following amounts were used: 0.75 mol % catalyst of (**R**)-ligand **T,** 10 mg of substrate, 17 hours at room temperature under 50 bar hydrogen pressure in 0.5 mL of DCM. The product was obtained as colourless oil in 94% yield with 100% conversion, R_f = 0.79 (pentane). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.53 (m, 2H), 7.33 (d, 2H), 2.87 (m, 1H), 2.04 (m, 1H), 1.64 (m, 8H), 1.06 (d, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 151.81, 127.50, 126.78, 125.35, 125.31, 125.28, 125.24, 77.48, 77.36, 77.16, 76.84, 39.82, 38.05, 35.98, 33.75, 31.96, 30.30, 29.04, 27.96, 26.17, 22.08, 21.12, 18.85. **IR** (NaCl, CCl_4, cm^{-1}): ν = 2958.37, 2927.39, 2853.94, 2295.64, 1702.82, 1549.81, 1326.53, 1257.03, 1217.61, 1130.08, 1006.41, 979.13
HRMS-CI: m/z: $[M]^+$ Calc. for $C_{14}H_{17}F_3$ 242.1282; Found 242.1293. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$ ($CDCl_3$, 0.141 $g.mL^{-1}$)= -7.80.
The enantiomers were separated with GC-MS with an Astec® Chiraldex-β-DM column (30m, 0.25 mm, d_f 0.12 μM), split ratio: 50, helium flow: 1 $mL.min^{-1}$, 85°C isothermal for 200 min. Peaks: 123 (cis), 128 (cis), 172 (trans, major) and 176 (trans, minor) minutes.

Entry 18:



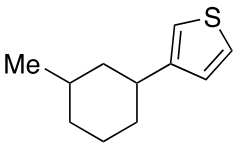
1,2-diethyl-4-methylcyclohex-1-ene, according to the general procedure, the following amounts wereused: substrate 20 mg, Ir-complex 2 mol%, CH2Cl2 1 mL, 50 bar pressure H2. Colorless oil. **1H NMR** (CDCl3, 400 MHz): δ 2.08-1.88 (m, 7H), 1.70-1.52 (m, 3H), 1.24-1.17 (m, 1H), 0.96-0.91 (m, 9H). **13C NMR** (CDCl3, 100 MHz): δ 130.85, 130.82, 37.75, 31.81, 29.39, 9.22, 25.94, 25.75, 22.18, 13.56, 13.47. **IR** (NaCl, neat, cm-1): ν = 3026.21, 2964.15, 2928.19, 2725.21, 2052.06, 1231.75, 1294.15. **HRMS-CI** m/z: [M]+ Calc. for C11H22 154.1721; Found 154.1736. $[\boldsymbol{\alpha}]\boldsymbol{D23}$ = -89.266, (*c* = 0.230, CHCl3). **GC-MS**: column Chiraldex-β-DM, 55oC isothermal, 1ml/min (He), t*R* = 39.1 min (minor)/40.1 min (major), 99% *ee*.

Entry 19:



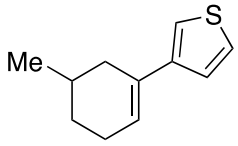
3,4',6-trimethyl-2,3,4,5-tetrahydro-1,1'-biphenyl. According to the general procedure, the following amounts were used: 1.00 mol % catalyst of (**R**)-ligand **V,** 10 mg of substrate, 17 hours at room temperature under 50 bar hydrogen pressure in 1.0 mL of DCM. The product was obtained as colourless oil in 97% yield with 100% conversion, R_f = 0.68 (pentane). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.26 (m, 2H), 7.15 (m, 1H), 7.09 (m, 2H), 2.33-1.99 (m, 3H), 2.90-1.65 (m, 3H), 1.51 (s, 3H), 1.32-1.19 (m, 1H), 0.94 (d, 3H).. **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 144.52, 132.00, 128.80, 128.58, 128.06, 125.94, 77.48, 77.16, 76.84, 40.72, 31.97, 31.47, 29.53, 21.89, 20.56. **IR** (NaCl, neat, cm^{-1}): ν =: 3147.85, 3076.39, 3020.43, 2949.67, 2911.00, 2829.59, 2726.16, 1943.13, 1743.51, 1662.77, 1599.50, 1489.89, 1377.06, 1259.59, 1070.36, 1026.92, 803.69. **HRMS-CI:** m/z: $[M]^+$ Calc. for $C_{14}H_{18}$; 186.1409; Found 184.1408. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$ ($CDCl_3$, 0.183 $g.mL^{-1}$)= -73.22.
The enantiomers were separated with GC-MS with an Astec® Chiraldex-β-DM column (30m, 0.25 mm, d_f 0.12 μM), split ratio: 50, helium flow: 1 $mL.min^{-1}$, 80°C isothermal for 200 min. Peaks: 152 (minor) and 157 (major) minutes.

Entry 20:



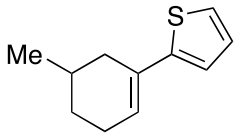
3-(3-methylcyclohexyl)thiophene. According to the general procedure, the following amounts were used: 1.00 mol % catalyst of (**R**)-ligand **T,** 10 mg of substrate, 17 hours at room temperature under 50 bar hydrogen pressure in 1.0 mL of DCM. The product was obtained as colourless oil in 44% yield with 79% conversion. **^{1}H NMR** ($CDCl_3$. 400 MHz): δ 7.24 (m, 2H), 7.00 (m, 1H), 6.95 (m, 1H), 2.95 (m, 1H), 2.24 (m, 1H), 2.04-1.28 (m, 8H), 0.99 (d, 3H) . **^{13}C NMR** ($CDCl_3$, 400 MHz): 141.65, 141.50, 138.46, 133.91, 131.48, 128.82, 128.79, 128.40, 128.13, 127.32, 127.29, 126.99, 126.74, 125.12, 124.41, 121.77, 118.06, 34.28, 33.03, 32.29, 29.87, 29.09, 28.45, 23.51, 23.06, 22.50, 21.69, 14.22. **IR** (NaCl, CCl_4, cm^{-1}): v=: 3049,12 cm^{-1}, 2926.52 cm^{-1}, 2853.10 cm^{-1}, 1551.37 cm^{-1}, 1458.18 cm^{-1}, 1377.51 cm^{-1}, 1264.22 cm^{-1}, 1218.63 cm^{-1}, 1009.09 cm^{-1}, $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$ ($CDCl_3$, 0.159 $g.mL^{-1}$)= - 8.18.
The enantiomers were separated with GC-MS with an Macherey-Nagel® Hydrodex-β-3P column (25m, 0.25 mm), split ratio: 50, helium flow: 1 $mL.min^{-1}$, 90°C isothermal for 100 min. Peaks: 77 (cis), 83 (cis), 85 (trans, major) and 89 (trans, minor) minutes.

Entry 21:



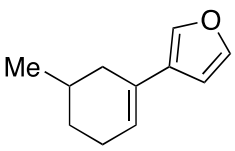
3-(5-methylcyclohex-1-en-1-yl)thiophene. According to the general procedure, the following amounts were used: 0.43 mol % catalyst of (**R**)-ligand **V,** 25 mg of substrate, 17 hours at room temperature under 50 bar hydrogen pressure in 1.0 mL of DCM. The product was obtained as colourless oil in 70% yield with 88% conversion, R_f = 0.68 (pentane). **^{1}H NMR** ($CDCl_3$. 400 MHz): δ 7.26-7.23 (m, 2H), 7.09 (t, 1H), 6.18-6.13 (m, 1H), 2.54-2.44 (m, 1H), 2.31-2.13 (m, 2H), 2.06-1.94 (m, 1H), 1.91-1.69 (m, 2H), 1.68-1.47 (m, 1H), 1.08-1.01 (d, J= 6.55 Hz, 3H) . **^{13}C NMR** ($CDCl_3$, 400 MHz): δ. 143.92, 131.59, 127.40, 125.16, 124.82, 124.77, 123.46, 117.84, 39.63, 35.90, 34.13, 33.79, 30.46, 28.81, 27.70, 25.69, 22.35, 22.01, 21.17, 14.07. **IR** (NaCl, CCl_4, cm^{-1}): v=: 3049.17, 2950.41, 2922.85, 2683.38, 1456.08, 1434.73, 1264.15, 863.92 $cm^{-1.}$ **HRMS:** m/z: $[M]^+$ Calc ;178.0828 Found ; 178.0816.$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ ($CDCl_3$, 0.342 $g.mL^{-1}$)= -26.901.
The enantiomers were separated with LC-SFC-MS with a Chiral Cell, 5% methanol and 95% CO_2 2 $mL.min^{-1}$. Peaks eluted at 8.8 (major) and 9.2 (minor) minutes.

Entry 22:



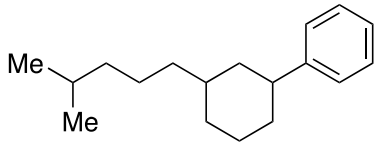
2-(5-methylcyclohex-1-en-1-yl)thiophene. According to the general procedure, the following amounts were used: 1.00 mol % catalyst of (**R**)-ligand **T,** 5 mg of substrate, 17 hours at room temperature under 50 bar hydrogen pressure in 1.0 mL of DCM. The product was obtained in to small conversion (13%) to determine or analyse anything, except for the conversion.

Entry 23:



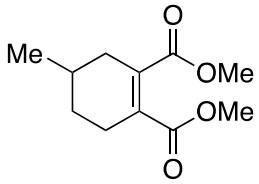
3-(5-methylcyclohex-1-en-1-yl)furan. According to the general procedure, the following amounts were used: 0.51 mol % catalyst of (**R**)-ligand **T,** 5 mg of substrate, 17 hours at room temperature under 50 bar hydrogen pressure in 1.0 mL of DCM. The conversion to the product was too low (31%) to determine or analyse anything, except for the conversion.

Entry 24:



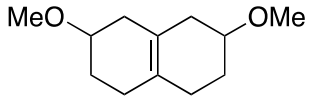
(3-(4-methylpentyl)cyclohexyl)benzene. According to the general procedure a racemic sample was prepared with palladium on carbon. The sample could not give a separation on any of the chiral columns.

Entry 25:



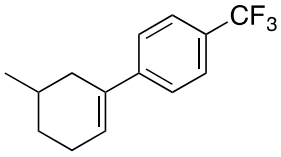
dimethyl 4-methylcyclohex-1-ene-1,2-dicarboxylate. According to the general procedure, the following amounts were used: 0.5 mol % catalyst of (**R**)-ligand **V,** 10.5 mg of substrate, 17 hours at room temperature under 50 bar hydrogen pressure in 0.5 mL of DCM. The product was obtained as colourless oil in 50% yield with 100% conversion, R_f = 0.4 (pentane: ethyl acetate, 15:1). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.01 (d, J = 6.59 Hz, 3H), 1.24 (m, 1H), 1.63 – 1.83 (m, 2H), 1.91 (m, 1H), 2.32 (m, 1H), 2.40 – 2.52 (m, 2H), 3.76 (s, 6H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 21.33, 26.54, 27.63, 29.53, 34.52, 52.27, 77.16, 135.22, 135.24, 169.09, 169.14. **IR** (NaCl, neat, cm^{-1}): v = 2952, 2927, 1723, 1650, 1434, 1262, 1067, 1025, 742. **HRMS-ESI** m/z: $[M+Na]^+$ Calc. for $C_{11}H_{16}O_4$ 235.0940; Found 235.0941. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$ ($CDCl_3$, 0.160 g. mL^{-1}) = -73.13.

Entry 26:



2,7-dimethoxy-1,4,5,8-tetrahydronaphthalene. According to the general procedure, the following amounts were used: 0.50 mol % catalyst of (**R**)-ligand **V,** 9 mg of substrate, 17 hours at room temperature under 50 bar hydrogen pressure in 0.5 mL of DCM. The product was obtained as colourless oil in 70% yield with 100% conversion, R_f = 0.68 (pentane). The substrate has been hydrogenated before in the group and the full characterization is reported[18].

Entry 27



3-methyl-4'-(trifluoromethyl)-2,3,4,5-tetrahydro-1,1'-biphenyl. According to the general procedure, the following amounts were used: 0.42 mol % catalyst C, 24.27 mg of substrate, 3 hours at room temperature under 5 bar hydrogen pressure in 1.0 mL of DCM. The product was obtained a colourless oil in 39% yield with % conversion, R_f= 0.81 (pentane). **^{1}H NMR** ($CDCl_3$. 400 MHz): δ 7.57-7.51 (m, 2H), 7.49-7.44 (m, 2H), 6.21-6.16 (m, 1H), 2.50-2.41 (m, 1H), 2.36-2.19 (m, 2H), 2.09-1.98 (m, 2H), 1.34-1.20 (m, 1H), 1.07 (d, J= 6.6 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 400 MHz): δ 146.00, 135.33, 126.63, 125.16, 125.12, 125.08, 125.04, 99.98, 35.83, 30.16, 28.90, 26.02, 21.93. **IR** (NaCl, CCl_4, cm^{-1}): v=: 3004.00, 2927.09, 2646.30, 1800.82, 1614.93, 1326.34, 1069.41, 1165.51, 1123.36, 825.70 cm^{-1} **HRMS:** Calc ; 240.1126 for $C_{14}H_{15}F_3$ Found ; 240.1140. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$ ($CDCl_3$, 0.194 $g.mL^{-1}$)= - 47.423. The enantiomers were separated with GC-MS with an Astec® Chiraldex-β-DM column (30m, 0.25 mm, d_f 0.12 μM), split ratio: 50, helium flow: 1 $mL.min^{-1}$, 85°C isothermal for 300 min. Peaks: 233 (major) and 242 (minor) minutes.

3.0 Results & Discussion

3.1 Ligand Synthesis

Since one of the aims for this project is to study the imidazole-based catalyst, a vast amount of analogue catalyst has been synthesized (Figure 3.1). The analogues were made by substitutions on the phenyl ring attached to the imidazole ring. The ligands have been synthesized according to the procedure in the original publication[4]. The original project idea included over 22 analogues. In most of these cases the isomers couldn't be separated with preparative HPLC or other synthetic problems arose. This thesis only shows the catalysts that worked. From now on the coherent catalysts have letters (T-Z, see Figure 3.1).

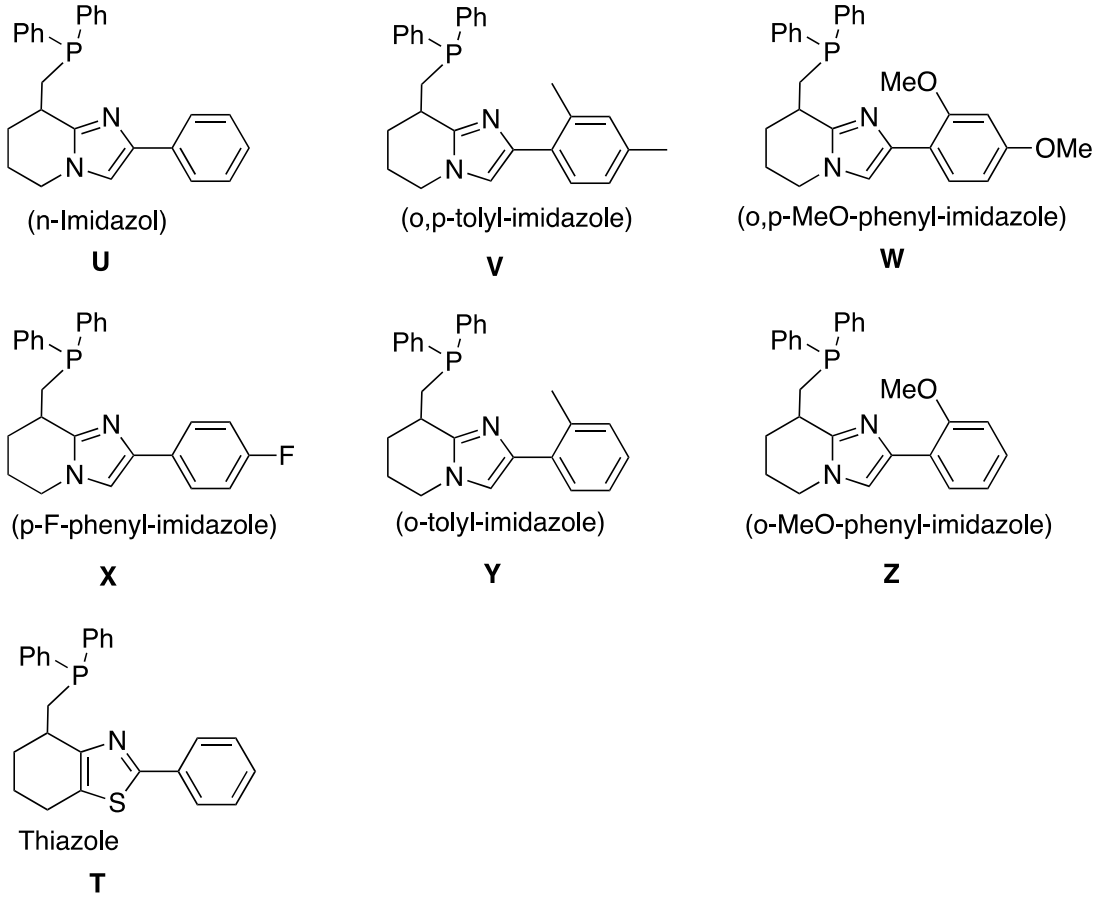
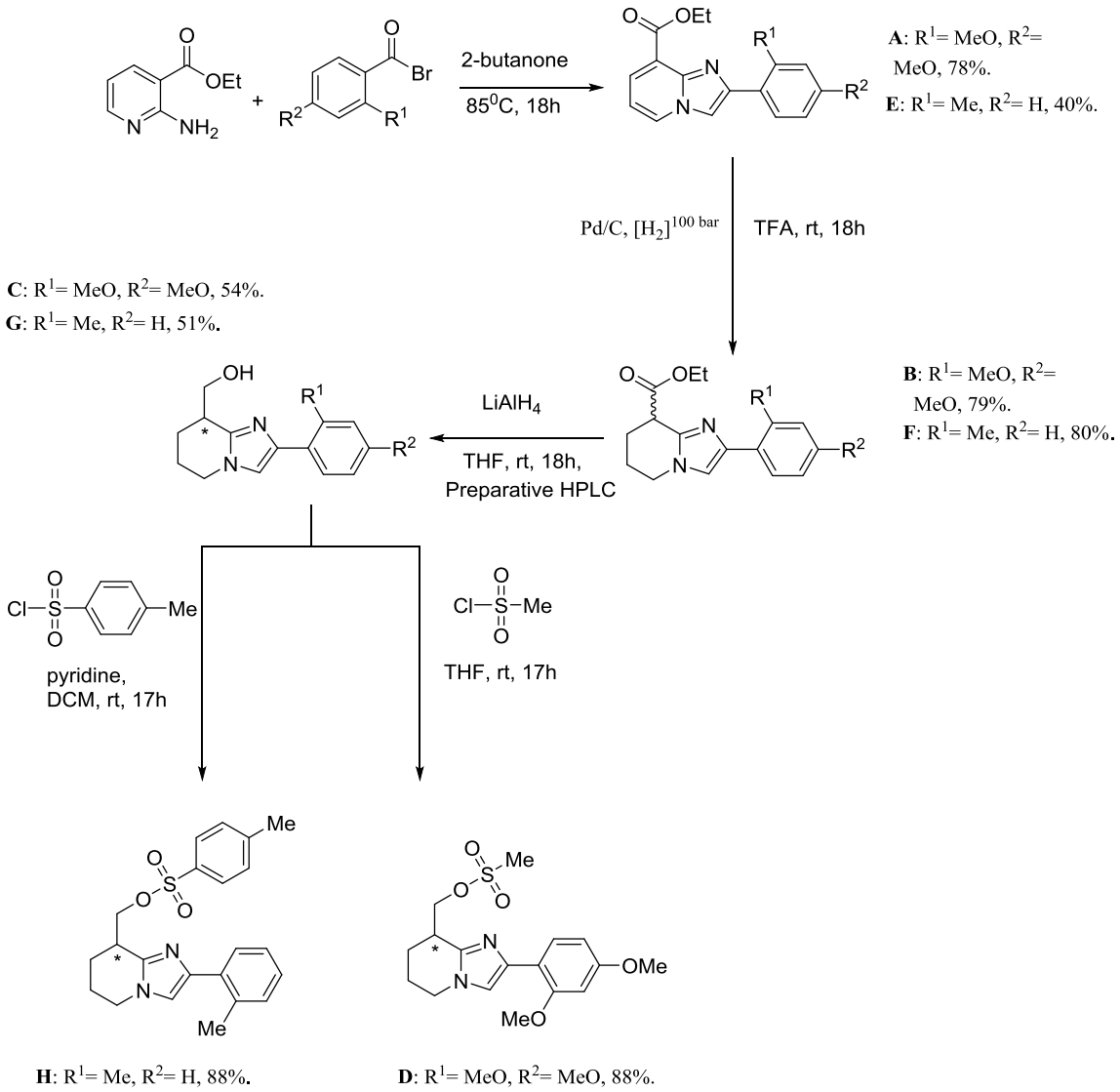


Figure 3.1. Novel analogue imidazole ligands obtained by the PGA-group.

In this thesis the first four synthetic steps of two-ligands will be described. The overall reaction scheme is shown in scheme 3.1. From now the ligand steps will have a letter to distinguish them, see reaction scheme.



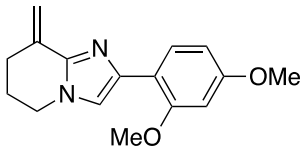
Scheme 3.1. Overall reactions scheme of the reactions performed in the ligand synthesis.

In the first-step of the ligand synthesis, a (Hantzsch type) cyclization occurs between a nicotinic ester (synthesized by a former group member[4]) and the wanted substitution on 2-bromo-acetophenon. Compound **A** was obtained in high yield after 18 hours of reaction time (78%). The reaction to form compound **E** could not reach completion according to TLC. The reaction was left for an additional night without success. The yield (46%) was low compared to the other ligands in this step. When the synthesis was repeated; similar yields, independent on the chemist, was obtained.
The dimethyl substitution gave 66% yield, which is low compared to other ligands (73-93%), the reason is most likely explained through steric-effects.

The next step is the reduction of the pyridine-ring. The reduction is performed with palladium on carbon (10 % w/w), 100 bar of hydrogen gas and 2,2,2-trifluoroacetic acid (TFA) as the solvent. TFA protonates the nitrogen in the imidazole-ring, protecting this ring from any hydrogenation and weakens the aromaticity in the pyridine-ring. This weakening will make the ring more susceptible to the reduction. Typically, strongly coordinating heteroatoms such as N and S, are known to compete with the double bonds for coordination to the Pd, thereby poisoning the Pd catalyst. Addition of a strong proton source sequesters the coordinating N-atoms in the imidazole substrate. Both intermediates could be obtained in good yield (79% and 81%) used without any purification step after the work-up.

In the next step towards the ligand the ester-group is reduced with $LiAlH_4$ to create an alcohol group attached to a chiral methyl-group. The enantiomers are separated with preparative-HPLC on a chiral column to obtain the pure enantiomers. The configuration of the enantiomers were assigned by comparison from the literature[5] (first peak is the (*R*)-configuration and the second is the (*S*)-configuration. Compound **C** and **G** were both obtained in good yield and pure enantiomers.

The next step is a sulfonation on the alcohol-group. This creates a good leaving group so that the intermediate can react with a phosphine to create the N,P-system. The sulfonyl used is tosyl chloride (p-toluenesulfonyl chloride). However, attempted phosphination on racemic **D** produced the elimination product (*see margin*). The reason behind this product is that the tosylated alcohol is too good of a leaving group[19]. None of the other five catalysts gave an elimination product in the above described step. To solve the elimination problem a sulfonation was performed with mesyl chloride (methylsulfonyl chloride). The mesyl group is also a good leaving group like the *p*-toluenesulfonyl, and is sometimes employed instead for steric and stability requirements. The reaction lead to intermediate **D** in 88% yield. Phosphination worked without elimination.



In order to streamline the synthesis of these catalysts, the synthesis was divided amongst the group members. Therefore, the phosphination, de-protection and complexation (see section 1.7) to form the catalysts, will not be mentioned in this thesis.

3.2 Substrate synthesis

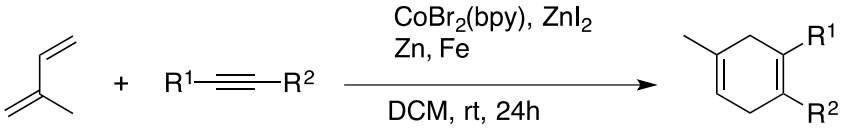
3.2.1 Cobalt-catalyst

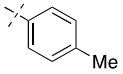
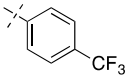
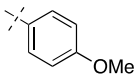
The synthesized $CoBr_2$(bpy) complex was analysed by determining the mass. Two similar intensities were detected however. These intensities arose from the bipyridine and the cobaltdibromide. The most likely reason for this phenomenon is that the ligand dissociated from cobalt in the mass spectrometer. Since the complex is paramagnetic it is not possible to analyse the complex by NRM-spectroscopy. Therefore the catalyst was tested in the reaction to determine if the complexation worked.

3.2.2 Diels-Alder reaction

According to the procedure[12] described by Hilt *et al* various (novel) 1,3-substituted cyclodiene substrates have been synthesized with 2-methyl-1,3-butadiene and mono or di-substituted acetylenes. Table 3.1 summarizes the substrates, obtained yield, reaction time and the substrate name, with this method.

Table 3.1. Synthesized substrates with the cobalt-catalysed Diels-Alder reaction with various acetylenes as starting material.



Entry number	R^1	R^2	Reaction time (hours)	Yield (%)
1	H		24	73
2	H		24	76
3	H		24	65
4			24	60
5			24	61
6	H		24	18
7	H		24	22
8	H		24	18
9			>72	0
10	H		>72	0
11	H		>72	>1

The low yields of **6, 7** and **8** can have two possible reasons. The heteroatom in the aromatic ring is retarding the reaction by weakly coordinating to the cobalt. The other explanation can be because of the decreased ring size. This heteroatom can coordinate to metals retarding the reaction. **9** gave no conversion that can be explained by the large nature of the two phenyl-rings on the acetylene. Hilt reported that the size of R^1 and R^2 determine the reaction time[12]. This would result in an extremely long reaction time which explains why no conversion could be observed after 72 hours.
Product **10** gave no conversion. Since nitrogen-containing aromatic-rings are coordinating to transition metals, acting as a Lewis base. This can result in no dissociation of the Co-N bond and rendering the catalyst unusable.

11 gave near to no conversion (>1%). One explanation can be steric hindering, when the cobalt-complex is trying to coordinate to the acetylene the methoxy group is too large and blocks the catalyst. Since both a methyl and a trifluoromethyl-group are larger in terms of steric hindrance[20,21] this explanation can be discarded completely because **2** gives the highest yield while having a larger steric hindrance site at the *para*-position. The explanation will probably lie in the electronic nature of the methoxy group, since a traditional Diels-Alder prefers an electron-withdrawing group close by the dienophile. The *p*-methoxy group in **11** donates too much electrons density to the overall system of the dienophile and almost completely prevents the reaction[15].

3.2.3 Changing the diene

When the Diels-Alder reaction was performed with 2,3-dimethy-1,3-butadiene and phenylacetylene no product could be observed in 48 hours. The change was made in order to synthesize a tetrasubstituted olefin When the butadiene was changed to myrcene (7-Methyl-3-methylene-1,6-octadiene) in the reaction with phenylacetylene, shown in figure 3.2, the product, now named **12** was obtained in 86% yield.

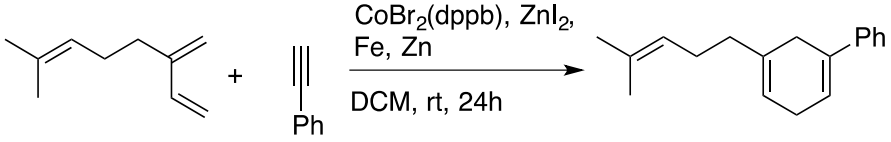


Figure 3.2. Reaction scheme of the Diels-Alder reaction with myrcene and phenyl acetylene.

3.2.4 Testing the *meta*-selectivity

NMR-spectroscopy confirmed the *meta*-selectivity of the catalyst. Since the cyclodiene products are mostly novel, reference ^{1}H NMR and ^{13}C NMR-spectra could not be found. It should also be mentioned that the differences in NMR shifts between the 1,3 and 1,4-products of the cyclodiene products are too close to draw certain conclusions. A few of the spectra of the analogue aromatic compounds are known[22]. By oxidizing the cyclohexadienes with DDQ (2,3-Dichloro-5,6-dicyano-*p*-benzoquinone) to the coherent aromatic compounds (Figure 3.3) the spectra could be compared to these known spectra in order to determine the main product.

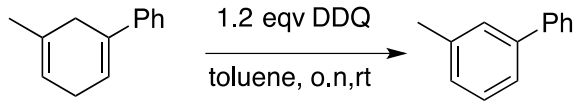


Figure 3.3. Reaction scheme of the oxidation of the cyclodiene to the aromatic product.

Products **1** and **4** were oxidized, ^{1}H and ^{13}C NMR-spectra were taken of the crude products, and from these results it was concluded that the major product of the $CoBr_2$(bpy) catalyst is the *meta*-product (1,3) as was reported.

3.2.5 Lewis-acid catalysed Diels-alder reaction

A Lewis-acid catalysed Diels-Alder reaction has been performed to make a tetra substituted Diels-Alder reaction product. The previously used method was not necessary to make this substrate since there is no line of symmetry in the product that can create a *meso*-compound after the hydrogenation.

Figure 3.4. Reaction scheme of the Lewis-acid catalysed Diels-Alder reaction.

Figure 3.4 shows the reaction scheme of the reaction. The product was obtained 50% yield after 18 hours. The substrate will be named **13** from now on.

3.2.6 Birch-reaction

A Birch-reduction was performed on 2,7-dimethoxynaphtalene to reduce this aromatic compound to the coherent bicyclic-triene.

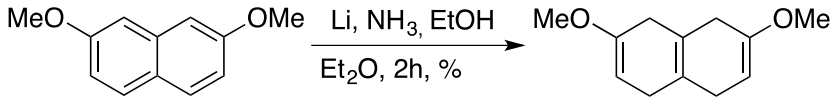


Figure 3.5. Reaction scheme of the Birch-reduction of 2,7-dimethoxynaphtelene.

The substrate could be synthesized in good yield (52%) and will be refer to as **14** from now on.

3.3 Hydrogenation results

The typical conditions for the hydrogenations were 0.5-1 mol% of iridium N,P-chelated catalyst, 50 bar hydrogen pressure and 17 hours reaction time in DCM as solvent. The exact conditions are given in the experimental section. Next to the novel catalysts synthesized by the group, the Ir-bound ligand[4] **U** was used as a reference. If no good ee or conversion could be obtained, the substrate was hydrogenated with the catalyst bearing ligand **T** as explained in the introduction, which is up to now still one of the better N,P- catalysts in the PGA-group[5]. The conversion and the cis/ trans ratio were determined by ^{1}H NMR while the ee was determined by analysing the products on the GC-MS with a chiral stationary phase.

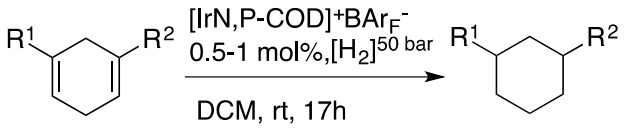
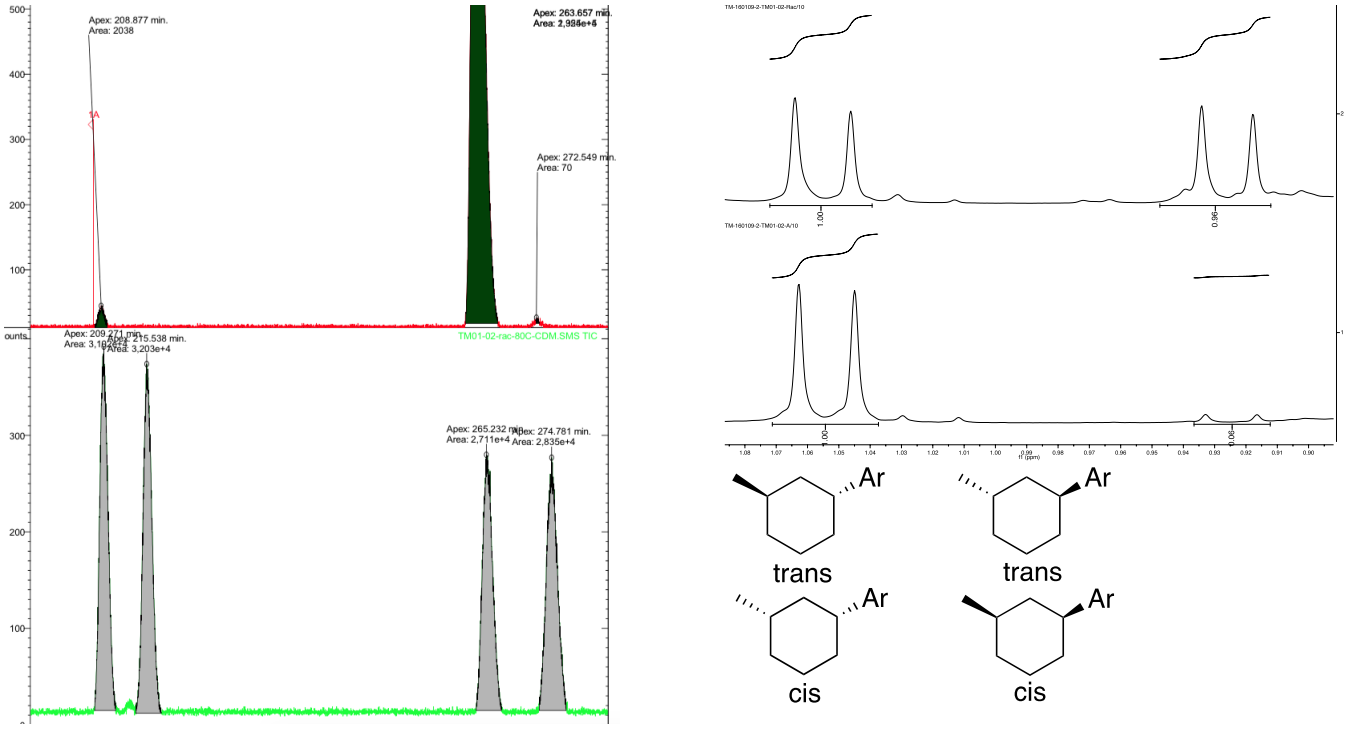


Figure 3.6. General reaction scheme for the hydrogenation of the synthesized trisubstituted olefins.

Figure 3.6 shows the general reaction scheme used in the hydrogenation of tri substituted olefins. The chromatogram of the racemic sample (with full conversion) shows four peaks (diastereomers), on the GC-MS. This results from the two pro-chiral centres on the substrates. Two of these peaks belong to the *cis*-isomer while the other two belong to the *trans*-isomer. The racemic sample makes it easy to determine which peaks in the chromatogram are the same stereoisomers. They will have the same area under the peak (see Figure 3.7). The conversion can be determined by comparing the ^{1}H NMR-spectra of the substrate with the hydrogenated product.



a) b) down c) up

*Figure 3.7. a) Chromatogram of **16**.* For specifications: see 2.8 entry 16. *b)Possible stereoisomers and enantiomers of the hydrogenation product. c) ^{1}H NMR-spectrum of racemic hydrogenated **16** (up) and chiral catalyst (down), enlarged on the discriminant for the cis/trans-ratio.*

<u>Formula to calculate the ee can be formulated as:</u>

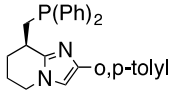
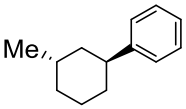
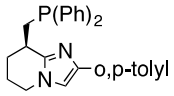
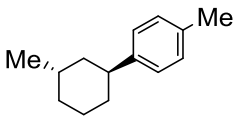
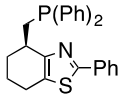
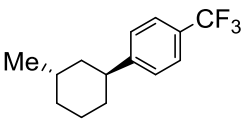
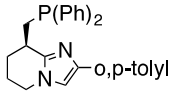
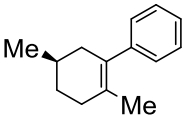
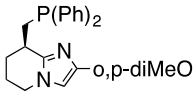
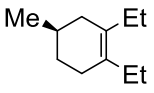
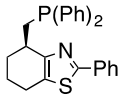
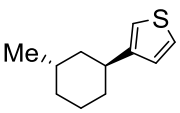
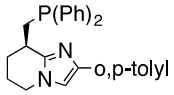
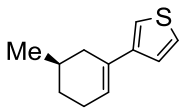
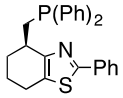
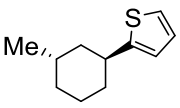
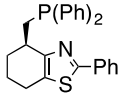
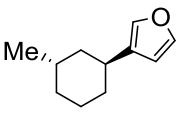
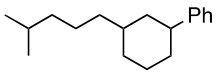
(formula 1) $$ee\ \% = \frac{N_1\ trans - N_2\ trans}{\Sigma N_{x,trans}} * 100$$

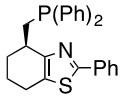
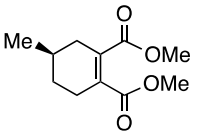
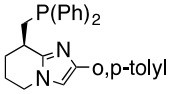
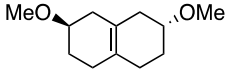
(N is the total area of one separated peak in the chromatogram, the same formula is also used for the cis-isomers).

The cis/trans-ratio is determined by comparing the doublets around 1.20-0.90 ppm[22] in the ^{1}H NMR-spectra. Since the cis/trans-isomers are asymmetrical, they have a different chemical environment and differ in chemical shift and thus the ratio can be determined (Figure 3.7 c). The trans-shifts are in general more downfield than the cis-shifts.

From the selectivity model it is predicted that the major product will be the trans-isomer (*see introduction: Selectivity Model*). This trend is also seen in Figure 3.7.

Table 3.2. Results from the hydrogenations of the synthesized substrates.

Entry	Substrate	Catalyst	Major product[a]	Conversion (%)	ee[b] (%)	Cis/trans-ratio
15	**1**	 **V**		100	99	3: 97
16	**2**	 **V**		>99	99	7: 93
17	**3**	 **U**		100	99	6: 94
18	**4**	 **V**		100	92	[c]
19	**5**	 **W**		100	99	[c]
20	**6**	 **U**		79	99	6: 94
21	**6**	 **V**		88	99	[c]
22	**7**	 **U**		13	-	3: 97
23	**8**	 **U**		31	-	-
24	**12**	*Pd/C and Crabtree's catalyst* [24]		-	-	-

25	**13**	 **U**		100	97	[c]
26	**14**	 **U**		100	99	2: 98

a: The determining of the absolute configuration will be shown in Results, section: Absolute configuration.
b: Determined by GC-MS, see 2.8 for conditions. The ee of the substrate is only screened if the major product described is obtained in abundance.
c: No cis/trans-ratio available since only one bond is hydrogenated.

The results in Table 3.2 shows that the catalyst can obtain high ee's and conversion for most of the substrates. The compounds will be divided in heterocycle free compounds and heterocyclic bearing compounds.

3.3.1 Heterocycle free compounds

The trisubstituted heterocycle free compounds could be obtained in good conversion and ee. The cis/trans-ratio was the major improvement, in most cases, between the previously described ligand **U** and the new analogues (**V-Z**). Improvements were seen in this ratio when the ee was already 99% with catalyst **U**.
When **3** was hydrogenated with catalyst **V** the conversion was low (59%). The substrate was majorly hydrogenated on the less hindered olefin bond as is predicted by the selectivity model[20]. This result will be further explored in *Results, section: 3.4 Selectivity Studies.*

The tetra substituted olefins are difficult to hydrogenate. The hindrance caused by the ligand around the catalyst blocks one of both groups attached to the olefin bond, as is seen in the four quadrants of the selectivity model. The most hindered catalyst **V** shows the best selectivity and ee for **18**. **19** only worked well with the much electron-rich **W** ligand. The coherent catalyst has smaller steric groups[21] than **V** but a much larger inductive effect. This effect can influences the bonding of the tetrasubstituted bond to the now more electron-rich iridium which possibly gives the selectivity for product **19**.

3.3.2 Heterocyclic bearing compounds

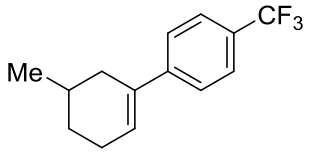
Lower conversion was obtained for the heterocyclic substrates (**6**, **7**, **8**) than the homocyclic compounds. The heterocyclic ring can coordinate on two possible ways to iridium[23]. The first possibility is through the π-system in the heterocycle, the latter through the heteroatom. In substrate **6** and **7** the heteroatom coordination has a relation with the thioether character of the sulphur atom. Since thiophene groups contain a small amount of thioether character[25] this will most likely cause the low conversion. The hydrogenation is strongly dependant on the position of the sulphur, when the substitution is on the 3'-position instead of the 2'-position there is a difference of nearly 66% conversion.

A clear regioselectivity can be observed when ligand **V** is used for substrate **6**. The olefin attached to the thiophene group does not hydrogenate well with this catalyst. This effect shows that the newly introduced steric groups on the phenyl ring block the thiophene ring and thus slow the coordination of the olefin.

In the case of **23** a conversion of 31 % can be reached. With higher H_2 pressure, elevated temperature and reaction time (100 bar, 24 hours, 40° C), it is possible to hydrogenate the furan ring[26] itself with a different class of ligands. However, it is the intention of this methodology to preserve the heterocyclic, therefore the imidazole catalysts fit well with this goal. The reported harsh conditions used to hydrogenation this class of substrate show that the oxygen coordinates with the catalyst.
Substrate **24** contains two pro-chiral centres. After hydrogenation this will result in two possible enantiomers. The substrate was hydrogenated with Crabtree's catalyst[24] and palladium on carbon at 50 bar for 17 hours. After the hydrogenation it was found that the stereo centres could not be separated on any of the chiral columns in the GC. When tried with chiral SFC it was found that the compound had too low a polarity and was not retained, eluting with the solvent front. Unfortunately, the compound could not be analysed after hydrogenation and was discarded.

3.4 Regioselectivity studies

Since the synthesized substrates have two double bonds, experiments were conducted in order to see if the hydrogenation could be stopped after hydrogenating one bond. It would be expected from the selectivity model that the less sterically hindered double bond would be hydrogenated first. The substrates chosen for this study are **3** and **4**. Substrate **4** already showed some selectivity when hydrogenated with ligand **V**.
Substrate **3** gave previously good results in terms of ee and conversion. The substrate also has the most steric hindered group (the shape of a CF_3-group is comparable with an isopropyl group[20, 21]). Furthermore, the CF_3-group is highly electron withdrawing what will result in a clear electron deficiency in the attached olefin bond. The deficiency retards the bonding to the iridium complex thus slowing down the hydrogenation of this particular bond. The partially hydrogenated product of **3** is shown in the margin and will be referred to as **27** from now on.

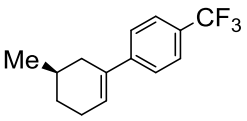
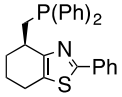
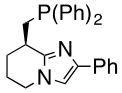
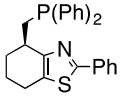
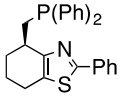
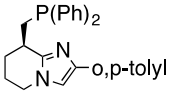
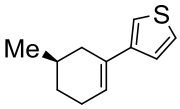
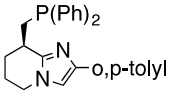
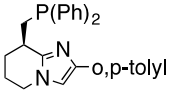
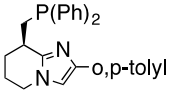


27

The hydrogen pressure and reaction time was adjusted to see if the reaction could be optimised. Furthermore, different solvents and additives were screened. The chosen solvents and additives were benzotrifluoride, benzene and additives K_3PO_4 and $KHCO_3$. The solvents were chosen based on their coordination ability to iridium, benzene>benzotrifluoride>DCM. The extremely weak coordination offered by DCM has proven to fit with the iridium hydrogenation chemistry. Where more strongly coordinating and bulky solvents retard catalysis.[9]

Table 3.3 summarizes the best results obtained with the selectivity studies. The conversions are determined by ^{1}H NMR. The remaining olefin protons of the starting material and the newly attached hydrogen atoms are used analyse this. There is a large shift (~3 p.p.m) between the newly arisen protons of the now saturated bond and the former olefin protons.

Tabel 3.3. Summary of the best results found with several selectivity study with the obtained major product, the catalyst used, hydrogen pressure, reaction time, additive and solvent.

Entry	Product	Catalyst	Conversion to the product (%)	H_2 pressure (bar)	Time (hour)	Additive	Solvent
1.1		 **T**	25	50	0.5	-	DCM
1.2		 **U**	9	50	0.5	-	DCM
1.3		 **T**	62	5	4	-	DCM
1.4		 **T**	72	5	4	K_3PO_4	Benz-CF_3
1.5		 **V**	88	5	3	-	DCM
2.1		 **V**	83	50	17	$KHCO_3$	Benz-CF_3
2.2		 **V**	79	50	17	$KHCO_3$	Benz
2.3		 **V**	88	50	17	-	DCM

Entry **1.1** and **1.2** shows nearly no selectivity. The hydrogenation is however quit fast. In case of imidazole ligand **U** the reaction is nearly to completion obtaining **17** a major product (91%) in 0.5 hours and **27** as minor product (9%).
When the results entries **1.1**-**1.2** and entries **1.3**-**1.5** are compared on the term of hydrogen gas, a trend is shown. When 50 bar hydrogen gas is used the major product will be **17** while a lower pressure leads to **27** as major product. This shows that the olefin containing *para*-trifluorotoluene is hard to hydrogenate.
A system of K_3PO_4 and benzotrifluoride give better selectivity towards product **27** when thiazole ligand **T** is used. The improvement is 10% than the thiazole **T** system of catalyst and DCM without additives.
The best selectivity to **27** can be obtained by using imidazole ligand **V**, 5 bar hydrogen gas, additives are not required and 3 hours gives the best conversion towards **27**.

As can be seen in table 3.3, entry **2.1**-**2.3** different solvents and additives give no better results in conversion to obtain **21.** The optimal reaction conditions are: 0.5 mol% catalyst, 50 bar hydrogen gas with imidazole catalyst **V** for 17 hours in DCM.

4.0 Conclusion

4.1 Ligand synthesis

The first four steps towards two novel ligands are shown in this thesis. The full catalysts could be prepared from the synthesized intermediates. In case of the ligand **W** an alteration had to be made to avoid an elimination product in the next synthetic step (see *Results & Discussion: ligand synthesis*). In the alteration mesyl chloride is used instead of the reported tosyl chloride.

4.2 Substrate synthesis

A large number of novel substrates have been successfully synthesized through published procedures. This includes some heterocyclic compounds. The heterocyclic bearing compounds clearly show a trend of lower yield than the other substrates. The published method does not work for nitrogen containing heterocyclic bearing compounds on the two-position or strongly electron donating groups like a methoxy-group. When the diene was changed to 2,3-dimethyl-1,3-butadiene no product was observed. A rational explanation for this phenomenon cannot be given.

4.3 Ligand studies

The substrates described in this thesis, as well as the other substrates in the manuscript of the full paper, show great affinity with ligand **V**. This will most likely be due to the fact of the steric hindrance caused by the newly introduced methyl-groups. This will enhance the enantio-selectivity by steric hindrance caused by the ligand on the metal. None of the other new synthesized ligands have shown as much promising results as ligand **V**.

When a substrate is used having very large side groups or coordinating heteroatoms, selectivity in the hydrogenation of the olefins could be improved using the sterically hindered imidazole ligand **V**. It was observed that this selectivity could happen quite fast and under mild conditions (up to 5 bar, 3 hours). In a single case the electron-rich ligand **W** turned out to be the superior ligand.

4.4 Hydrogenation and catalyst screening

Most of the substrates could be hydrogenated in good ee and cis/trans-ratio. The hetero-cyclic compounds had some troubles. In the thiophene containing compounds the conversion was related to the position of the sulfur. The closer the sulfur is to the catalyst the less conversion was obtained. This gave a good selective hydrogenation on the 3-position with catalyst **V**. The more electronegative furan substrate showed a poor conversion even when it was situated far from the olefin, where the reaction occurs. The main goal of creating a facile, and enantioselective strategy has been obtained.

4.5 Recommendations for further research

A lot of research has been done in the asymmetrical hydrogenation of cyclohexadienes. It is said that the tendency of asymmetric hydrogenation is to improve the substrate scope This should be pursued off course. It would be interesting to do further research in to the asymmetrical hydrogenation of heterocyclic-compounds.

In addition the N,P-chelated imidazole catalysts should be studied more. The phenyl-groups attached to the phosphine group can be studied in the future. When the results from this thesis are considered the focus should be on the electron-rich groups, like the dimethoxy-ligand **W**. In the past, toluene-phosphine groups[4] have already been researched and gave good results.

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Attachment 1: Example GC-MS Chromatogram of hydrogenated product

Print Date: 05 Feb 2016 12:25:31

Chromatogram Plots

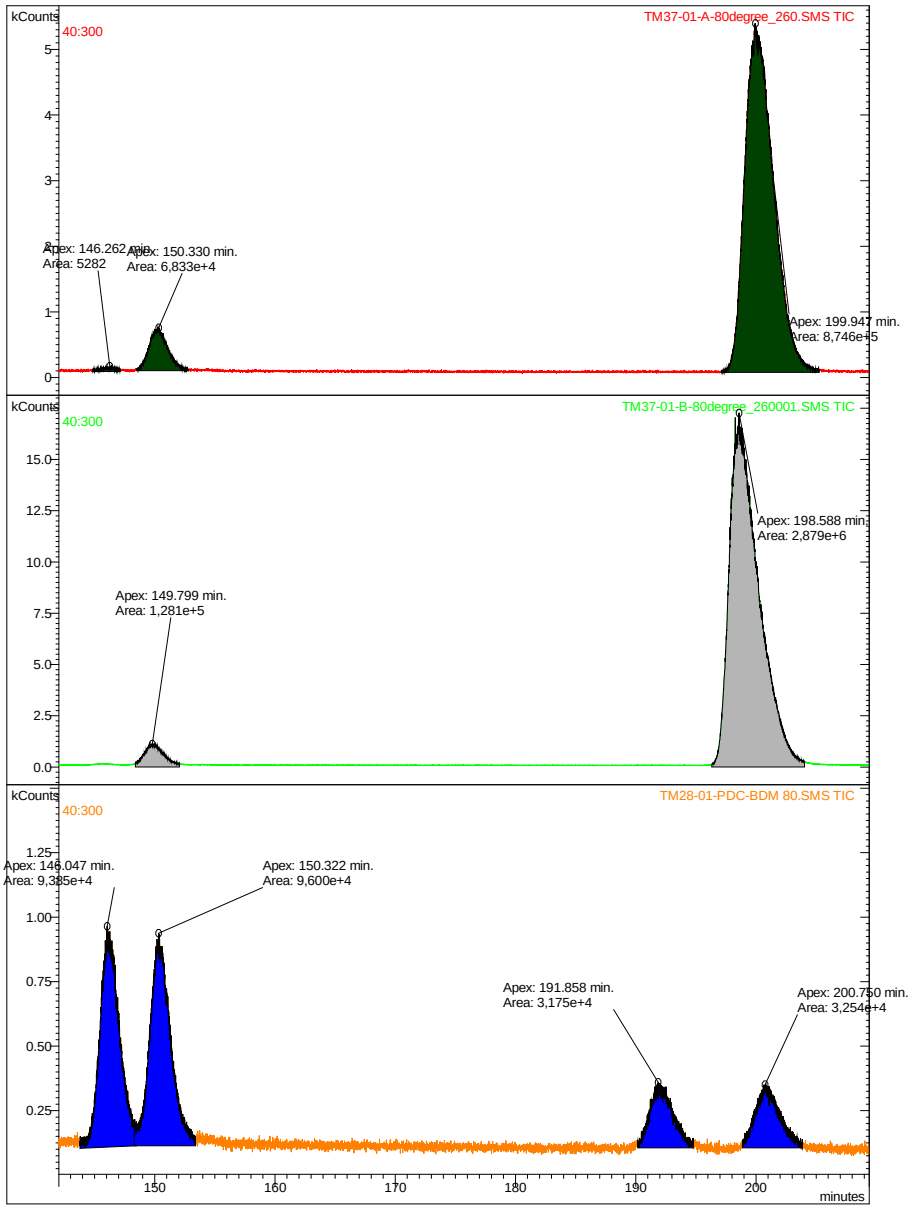

*Figure 4.1. Chromatogram of Entry **20**. From top to bottom: Ligand **U**, **T** and a racemic sample made with palladium on carbon. For conditions see: Experimental Hydrogenations; section 2.8.*

Attachment 2: Example NMR-spectra of Substrate

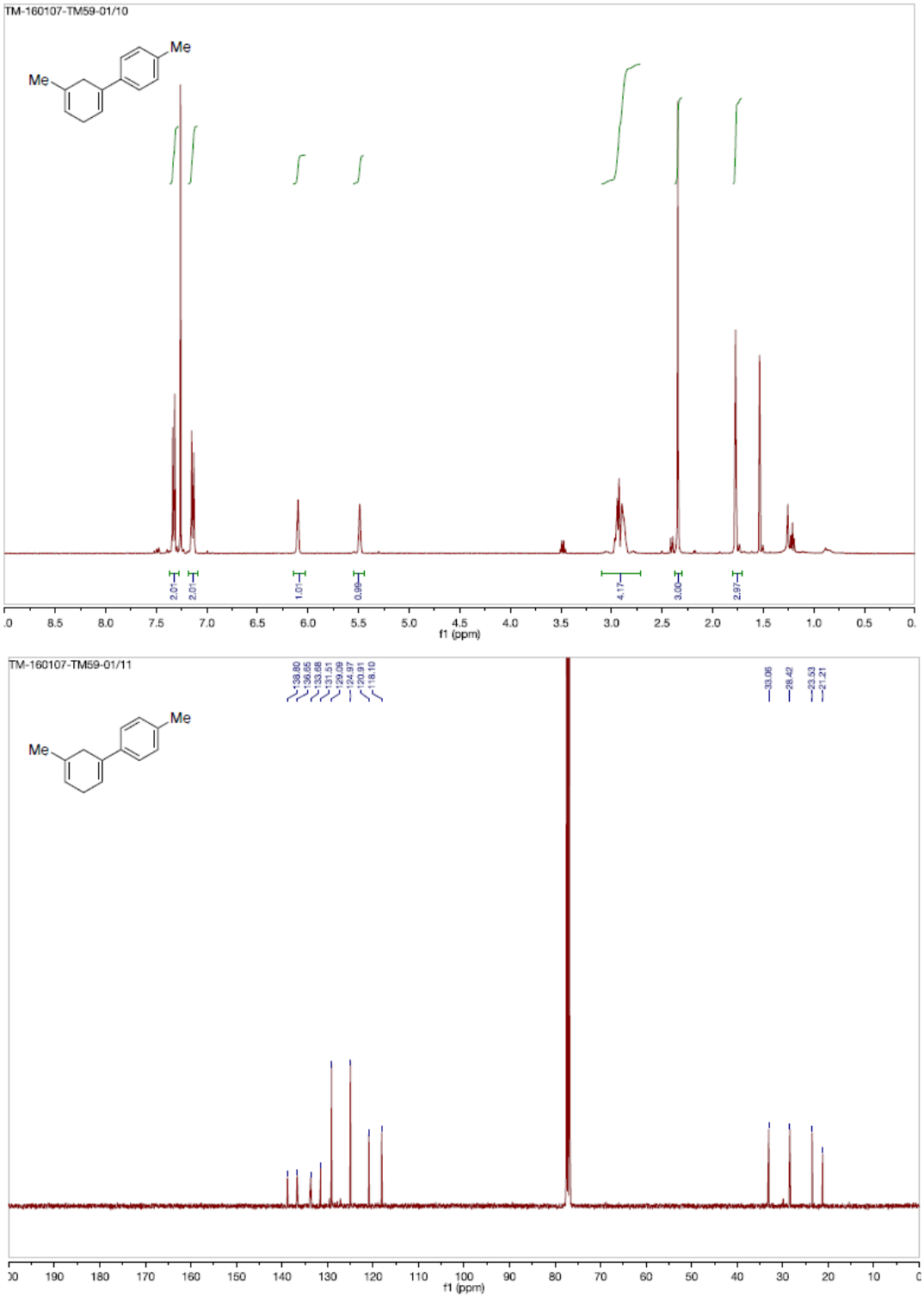

Figure 4.2. ^{1}H NMR- and ^{13}C -spectrum of substrate **2**. *A Bruker 400 MHz spectrometer has been used.*

Attachment 3: Example NMR-spectra of hydrogenated product

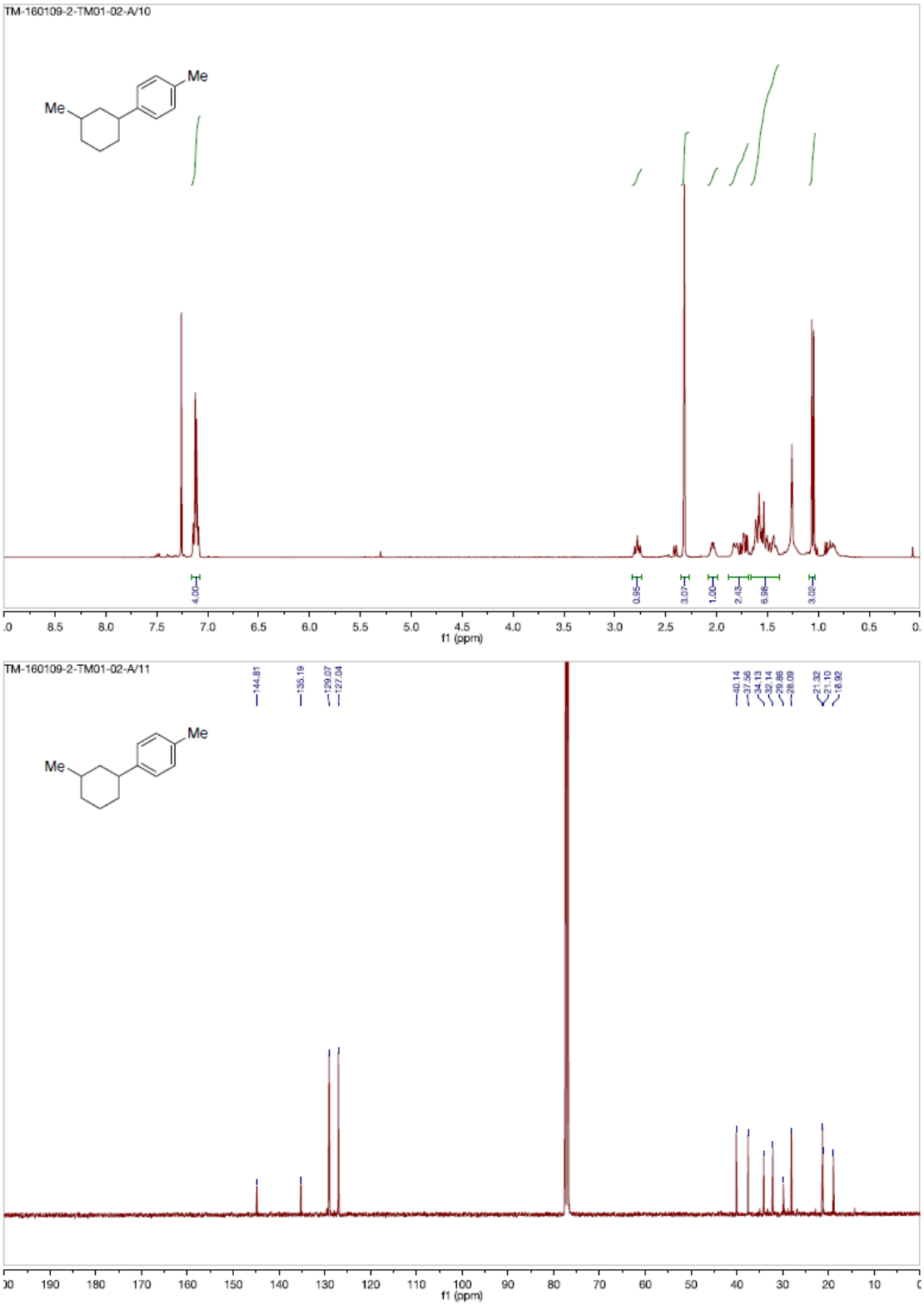

Figure 4.3. ^{1}H NMR- and ^{13}C -spectrum of substrate **16**. *A Bruker 400 MHz spectrometer has been used.*

Attachment 4: Example NMR-spectra ligand synthesis

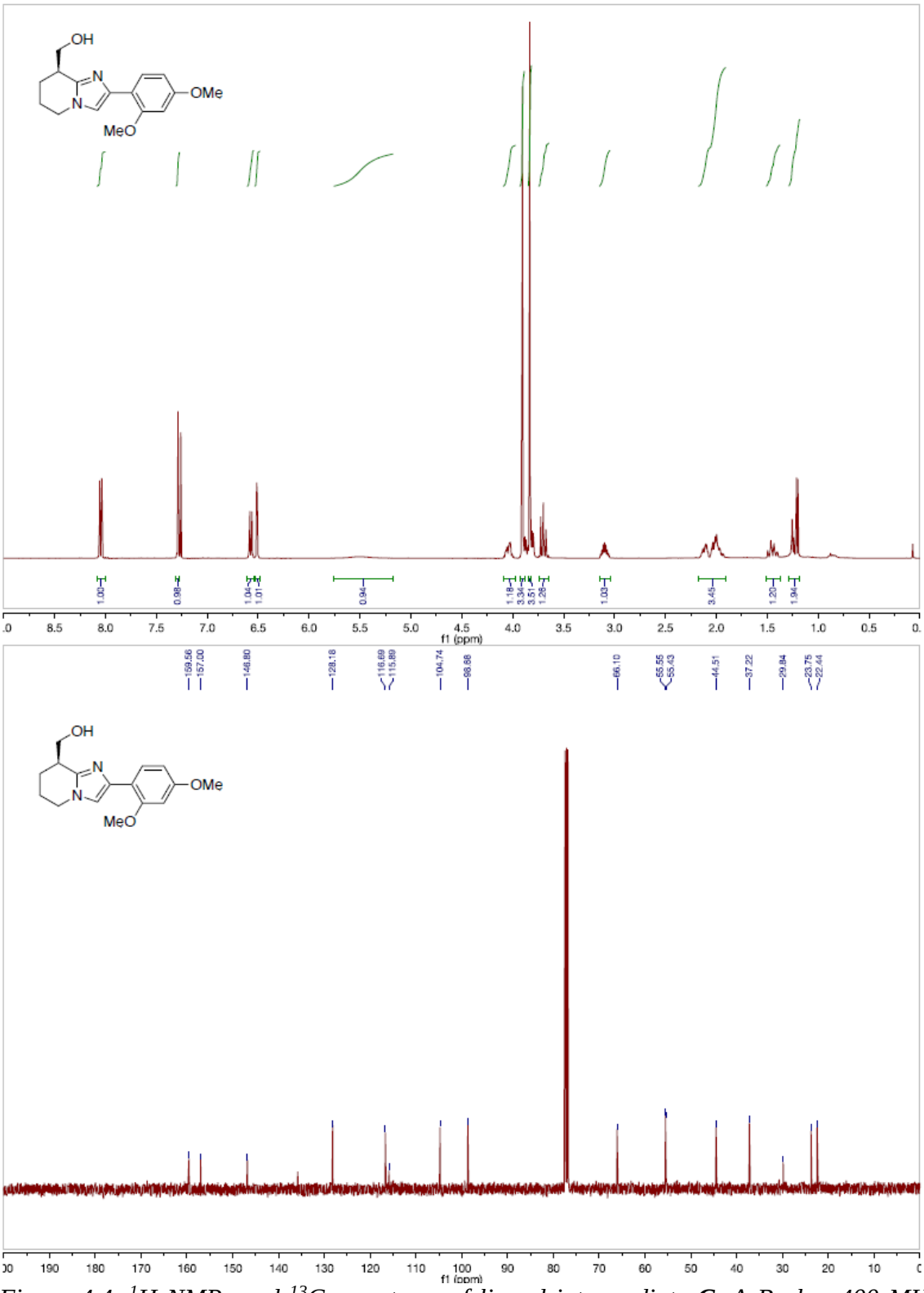

*Figure 4.4. ^{1}H NMR- and ^{13}C -spectrum of ligand intermediate **C**. A Bruker 400 MHz spectrometer has been used.*