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Synthesis and metal complexes of C2 symmetric ligands obtained from *R*-(+)-Betti and dialdehydes for asymmetric induction reactions

Tesi di laurea sperimentale

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Abstract

The aim of this master's research thesis was the employment of an enantiopure 1,3-aminoalcohol, the 1-(α-aminobenzyl)-2-naphthol, known as Betti base, for the synthesis of some novel compounds which show a C2 symmetry. Some of these compounds, after derivatization, were used as ligands in association with transition metals to prepare some catalysts for enantioselective catalytic reactions. Some aminoalcohol (Salan-type) derivatives of these compounds were obtained upon reduction and in some cases it was possible to obtain complexes with transition metals such as Mn, Ni, Co and Cu. Furthermore a novel 6-membered analogue bisoxazoline ligand, 2,6-bis((*R*)-1-Phenyl-1*H*-naphtho[1,2-*e*][1,3]oxazin-3-yl)pyridine, was obtained and from it two Cu-complexes were prepared. The metal complexes were employed in some reactions to test the asymmetric induction, which was in some cases up to discrete values.

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Synthesis and metal complexes of C2 symmetric ligands obtained from *R*-(+)-Betti and dialdehydes for asymmetric induction reactions

Introduction

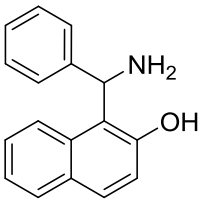
Enantiopure compounds are products with a high added value since biological systems, in most cases, recognize a pair of enantiomers as different substances which lead to unequal responses in the organism. Thus, one enantiomer may act as a very effective therapeutic drug whereas the other enantiomer may be highly toxic. Indeed, it has been shown for many pharmaceuticals that only one enantiomer contains all of the desired activity and that the other is either totally inactive or toxic. Hence, in the past decades, the importance to obtain enantiomerically pure or enantioenriched compounds has been fully acknowledged in synthetic chemistry, natural product synthesis, medicinal chemistry, agricultural and pharmaceutical industries. This happened especially after the Food and Drug Administration (FDA) issued regulations on "chiral drugs" which, since 1992, encourages the marketing of drugs as a single enantiomer.[1] Indeed the pharmaceutical companies are now obliged to conduct the clinical, pharmacological and toxicological studies on both the enantiomers to get the FDA's approval for the sale of the racemate, resulting in an economical disadvantageous process if the studies have to be conducted on both of them.[2] Anyway it is necessary to underline the fact that for the drugs developed and approved before the regulations became effective it is possible to sell the racemate if its toxicity is not proven.

In the pharmaceutical industry the drugs that are synthesized have one or more stereogenic centers which give to the various enantiomers or diastereoisomers of the particular compound the possibility to interact in a different manner with other molecules. This leads to the fact that only one enantiomer is the real, active drug (the eutomer) with the other enantiomer that doesn't react at all, in the best cases, or leads to undesired collateral effects in the worst (the distomer). It is hence easily understandable that is always desirable to obtain just the enantiomer of interest, especially when the products show a high cost for their synthesis and for the subsequent clinical trials like in the pharmaceutical industry. Readily available enantiomerically enriched molecules, obtained through enantioselective synthesis or from natural compounds, are the starting

materials for building single enantiomers of chiral target molecules. Sometimes, when a stereogenic carbon atom is present in the molecule, the subsequent reactions can be performed in a stereocontrolled way, exploiting just the preexistent chirality. On the other hand, often it is necessary to use enantiopure catalysts or reagents to achieve the desired stereochemistry. Enantioselective synthesis and catalysis have thus gained progressive importance in the past decades as the main ways to obtain these enantiopure compounds of interest.

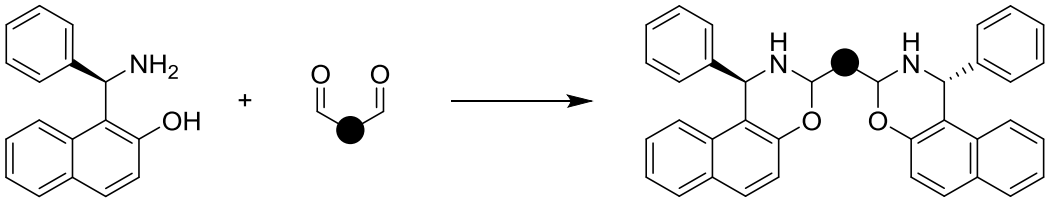
Aim of the project

The aim of my master's research thesis was the employment of an enantiopure 1,3-aminoalcohol, the 1-(α-aminobenzyl)-2-naphthol [**1**], known as Betti base,[3] for the synthesis of some novel compounds which would have shown a C2 symmetry and that theoretically seemed to be suitable, in some cases after eventual derivatization, for an use of them as ligands in association with transition metals to prepare some possible catalysts for enantioselective catalytic reactions.



(±) [**1**]

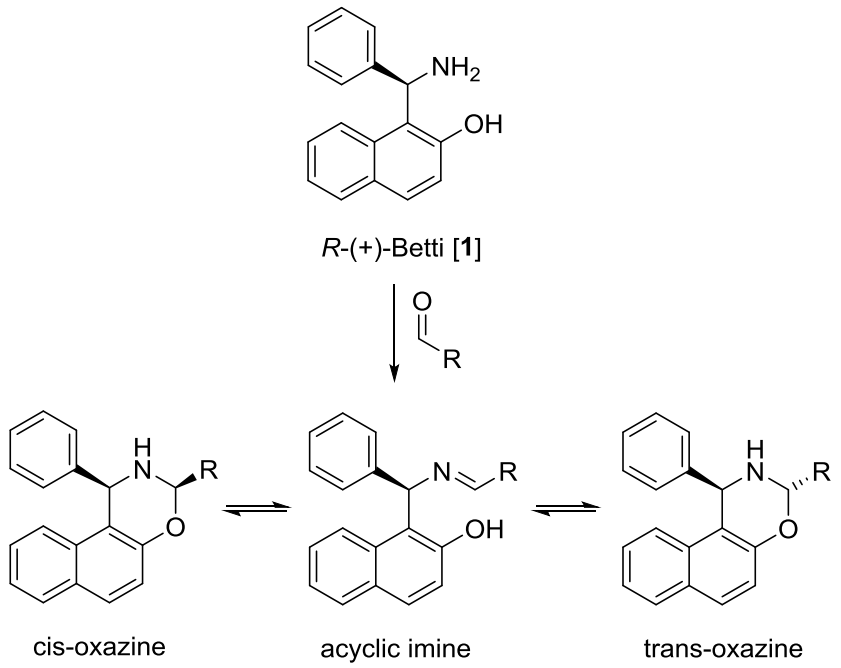
Thus through reaction of two molecules of enantiopure (*R*)-Betti base [**1**] and one of a dialdehyde seemed to be possible to obtain the desired compounds (figure 1).



R-(+)-Betti [**1**]

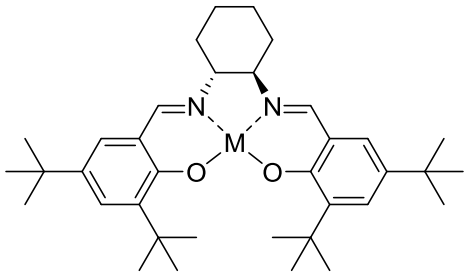
(figure 1)

It is well known from many previous works[4] that Betti base reacts with an aldehydic functional group to afford, in very good yields, the corresponding [1,3]-oxazines. They exist as a mixture of a cis- and a trans- (more stable) isomer which are in equilibrium with the acyclic open iminic form (figure 2).[5, i]



(figure 2)

For these reasons the target compounds seemed to be good candidates for the preparation of Salen-type catalysts (figure 3), if the compounds can bind the metal through their acyclic forms.

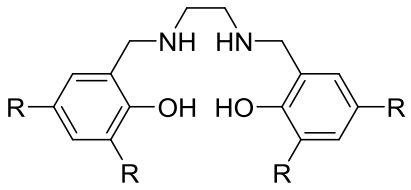


Salen catalyst

(figure 3)

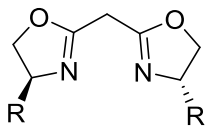
[i] from now on when talking about cis and trans isomers we will always refer to the relative stereochemistry of the two substituents on the same oxazinic ring (as shown in figure 2) since the stereochemistry will become more complicated when we will talk about compounds bearing two oxazinic moieties.

Furthermore, upon reduction of these compounds it should have been possible to obtain some Salan-type ligands (figure 4), or, on the other hand, after regioselective oxidation of them, some 6-membered ring bisoxazoline ligands (figure 5) analogues should have been possibly synthesized. In the end, the reaction of these derivatives with a transition metal should have led to the obtainment of the desired metal complexes to test them as possible enantioselective catalysts.

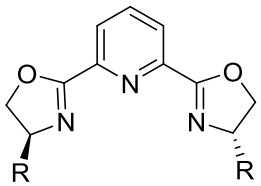


(Salan ligands)

(figure 4)



(BOX ligand)

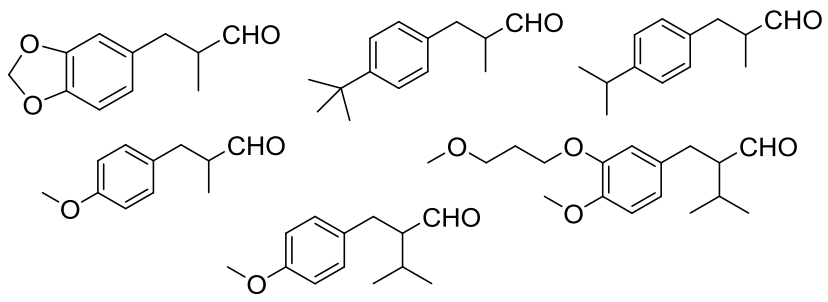


(PyBOX ligand)

(figure 5)

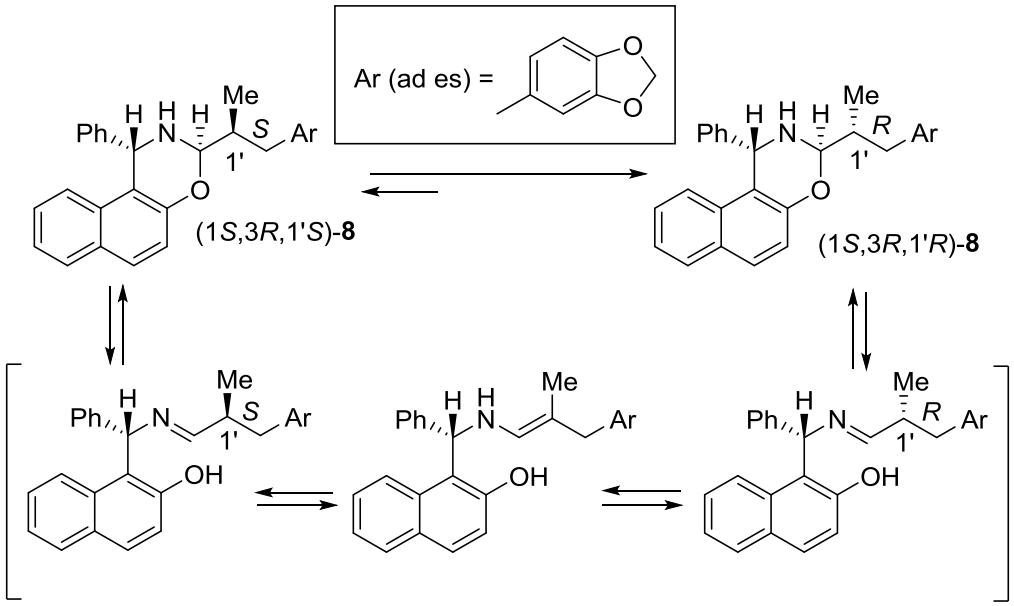
Betti base as an enantiopure chiral auxiliary

In this research project the enantiopure Betti base was chosen as the starting material for the preparation of the various ligands because it was already used in the same laboratory for the resolution of dihydrocinnamic α-substituted aldehydes(figure 6), through a process called crystallization induced diastereoisomeric transformation (CIDT) (figure 7).[6]



(figure 6)

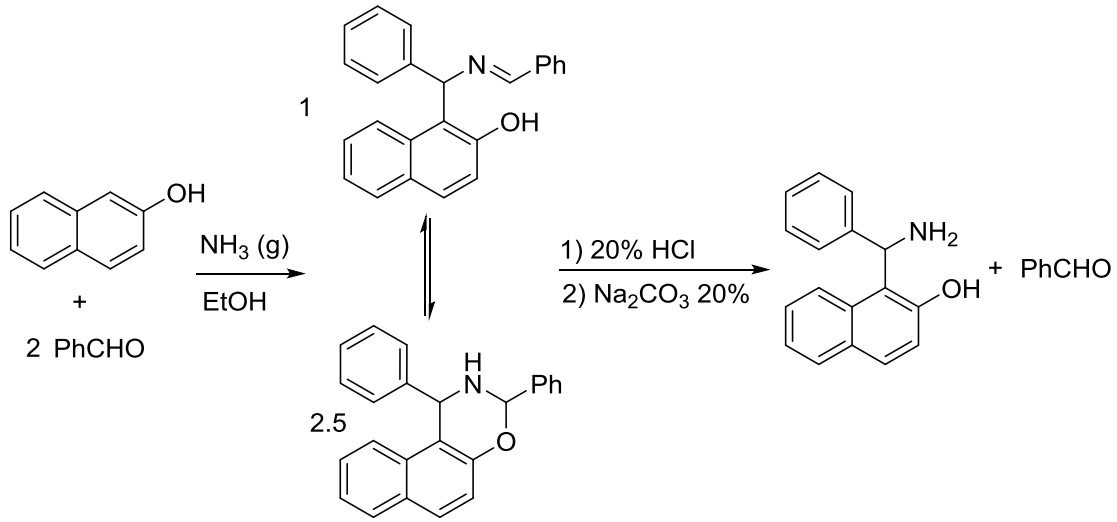
The latter exploits the different solubilities of the diastereoisomeric oxazines prepared by reaction of the enantiopure Betti base with racemic chiral aldehydes, leading to the preferential crystallization of one of the two diastereoisomers.



(figure 7)

Furthermore, although the 1-(α-aminobenzyl)-2-naphthol (Betti base) and its derivatives have been known since the beginning of the twentieth century, when Mario Betti reported the synthesis of it starting from 2-naphthol, benzaldehyde and ammonia, only recently there has been an increasing interest in using this chiral compound.[7] This is due to a relatively recent method for the kinetic resolution of racemic mixtures of Betti base which has been published in 2005 by Hu's research group[8] and that has allowed the easy obtainment of the two enantiomers of the base. Subsequently the various Betti base derivatives have been increasingly used in organic synthesis as chiral catalysts, enantiopure ligands, chiral auxiliaries and solvating reagents in ^{1}H NMR spectroscopy.[7]

Betti base preparation[3] (figure 8)



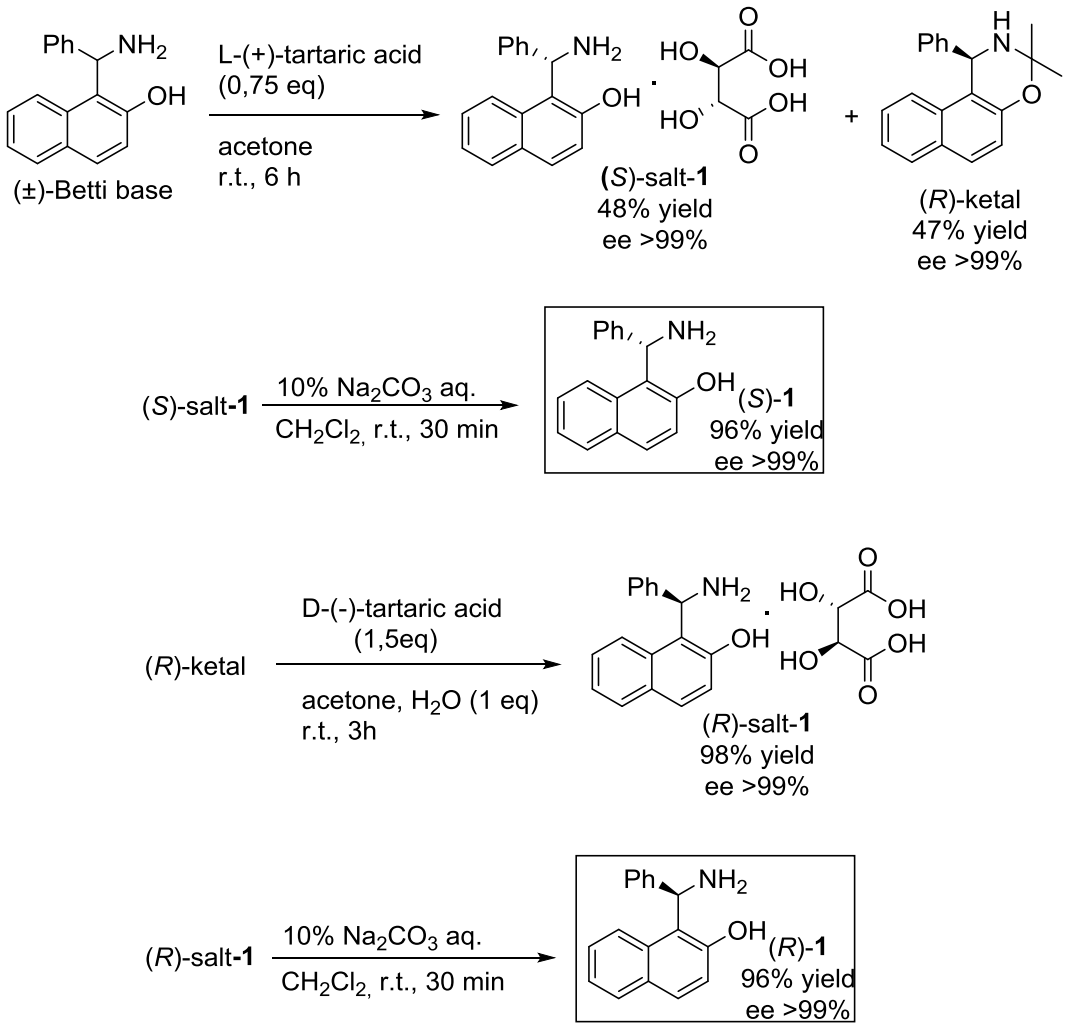
(figure 8)

Resolution of a racemic mixture of the Betti base[8]

The method for the resolution of Betti base into its two enantiomers mentioned above is based on an enantioselective *N*,*O*-deketalization achieved using enantiopure tartaric acid as chiral acid and ligand (figure 9). In the beginning, indeed, the resolution of this aminoalcohol was conducted using tartaric acid in ethanol but didn't lead to good yields and good enantiomeric excesses. This happens because in protic solvents the Betti base spontaneously gives a retro-Mannich reaction which leads to the formation of byproducts even at room temperature. Thus it was tried to perform the resolution in aprotic solvents, and, when acetone was used as solvent, it was observed the formation of a tartrate salt of one enantiomer of the Betti base and the formation of a *N*,*O*-ketal compound of the other enantiomer.

Working in acetone, the resolution of a racemic mixture of the Betti base undergoes three different stages where L-(+)-tartaric acid plays a different role in each of them. As a normal acid it promotes an acid catalyzed *N*,*O*-ketalyzation between the Betti base and the acetone, leading to the obtainment of the racemic *N*,*O*-ketal compound as the first pitchy precipitate. Subsequently, as a chiral acid, the L-(+)-tartaric acid catalyzes an enantioselective *N*,*O*-deketalization of the (*S*)-ketal compound leading contemporarily to the formation of the tartrate salt of the (*S*)-Betti base enantiomer as the second precipitate

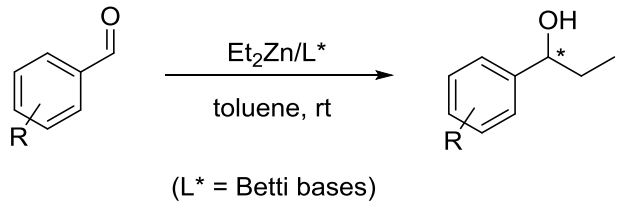
observed. Successively the (*R*)-Betti-salt can be obtained through treatment of the filtered (*R*)-ketal compound with D-(-)-tartaric acid.



(figure 9)

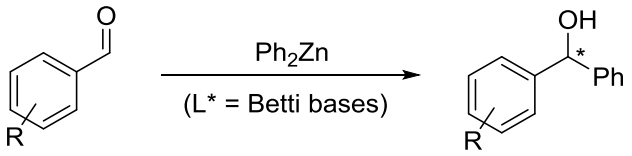
Application of Betti base and Betti base derivatives in asymmetric catalysis

The first application of aminobenzylnaphthols in asymmetric synthesis is an enantioselective addition of diethyl zinc to aryl aldehydes that was published in 1999 (figure 10).[9]

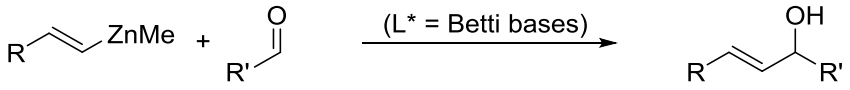


(figure 10)

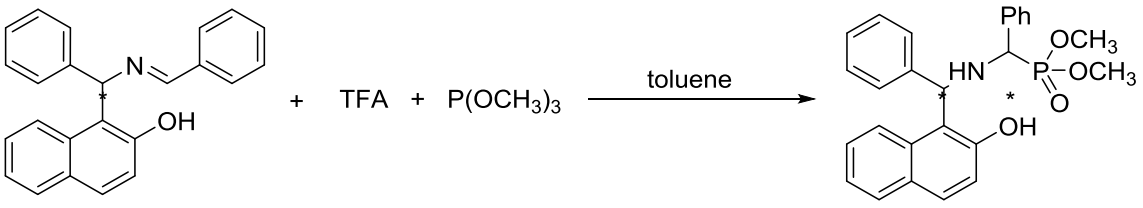
After that, many research groups have investigated the potential use of this kind of ligands to induce some enantioselectivity in organic reactions but the amount of works published remains scarce.[7] Applications of Betti base and its derivatives in the alkenylation and arylation of aldehydes were subsequently reported[10, 11 , 12] (figures 11 and 12) and 1-(α-aminobenzyl)-2-naphthol was used as a chiral auxiliary for the synthesis of enantiopure α-aminophosphonic acids (figure 13).[13]



(figure 11)

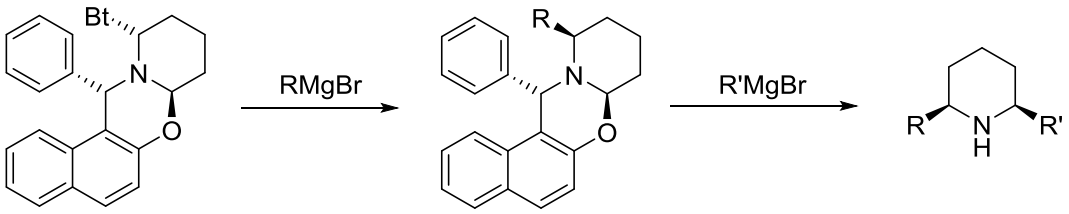


(figure 12)



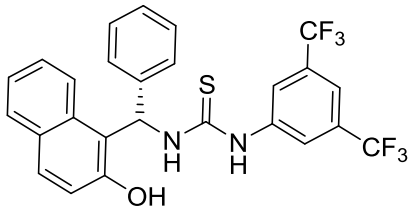
(figure 13)

Furthermore, Betti oxazines can be subjected to regio- and stereoselective arylation with Grignard reagents[14,15,16] to afford, after *N*-debenzylation, 2,6-disubstituted piperidines bearing one alkene- or alkyne-containing substituent which are useful precursors for the total synthesis of natural occurring alkaloids (figure 14).[17]

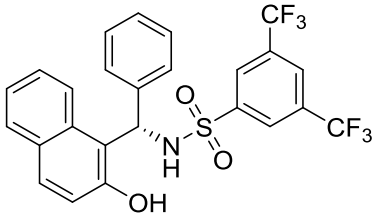


(figure 14)

A chiral phosphine ligand derived from this base was employed in a Tsuji-Trost palladium-catalyzed allylic substitution to test the asymmetric induction.[18] Moreover, Betti bases were employed in the separation of enantiomers of racemic ligands[19] and as chiral solvating reagents in ^{1}H NMR spectroscopy to evaluate the enantiomeric excess of chiral carboxylic acids.[20] A bifunctional thiourea organocatalyst prepared from it was employed in an asymmetric acyl-Strecker reaction (figure 15),[21] while a Betti derived sulfonamide catalyst was used in an asymmetric hetero Diels-Alder reaction (figure 16).[22]

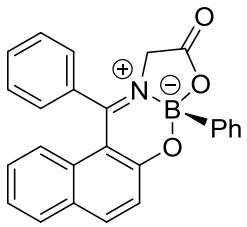


(figure 15)



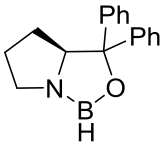
(figure 16)

Furthermore, the asymmetric synthesis of a boronate complex (figure 17) stereogenic exclusively at the boron atom has been achieved from enantiopure Betti base through chirality transfer from the carbon stereocenter that has been subsequently abolished.[23]



(figure 17)

Finally, during my bachelor internship, we tried to synthesize an enantiopure Betti base-borane complex which we thought could be used as a catalyst for enantioselective reduction of ketones to secondary alcohols. This was tried because we wanted to prepare a 6-membered ring analogue of the CBS-catalyst,[24] an oxazaborolidinic catalyst (figure 18) very useful for this enantioselective reduction. Thus we employed the (*R*)-Betti, which is a 1,3-aminoalcohol, to prepare this hypothesized compound, instead of a 1,2-aminoalcohol which is used to synthesize the oxazaborolidinic catalyst. Even if we weren't able to properly characterize the hypothesized catalytic complex, probably due to the existence of various different species in our reaction mixture, some reductions of prochiral ketones were tested. In many cases an asymmetric induction was observed with enantiomeric excesses up to 38%.



(figure 18)

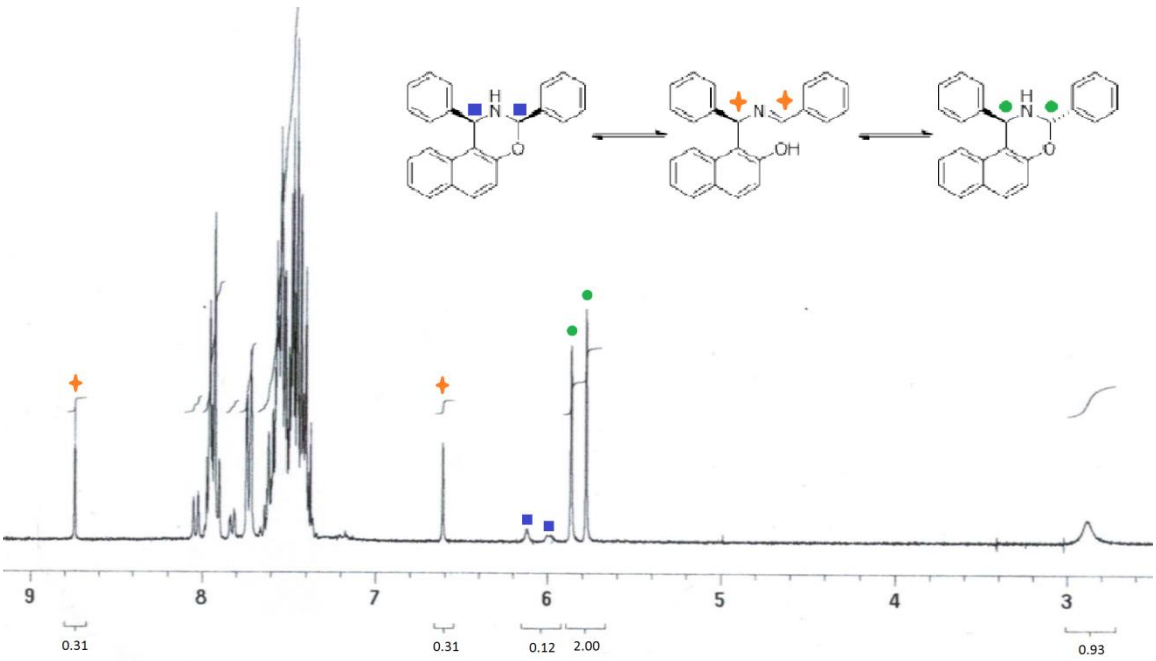
Preparation of the target molecules

Although many publications regarding the reaction of Betti base with various aldehydes were reported,[4] to the best of our knowledge, the use of a dialdehyde instead of a mono-aldehyde was present in few publications.[25,14,16,17].

First of all it is important to underline that when a molecule of Betti base reacts with an aldehyde the product can exist, in equilibrium, as cis- and trans- ring-closed isomers but also, in some cases, as an iminic acyclic form (figure 2). The ratio of the various species is substrate and substituent dependent and a quite exhaustive article regarding this topic has already been published.[5]

Hence, even in the case of the reaction of two molecules of Betti base with one of dialdehyde is reasonable to assume that many different species will be present at the equilibrium: cis- and trans- oxazinic isomers, iminic forms but also mix of them since two different 6-membered rings are formed in this step.

Anyway, from the observation of the various ^{1}H NMR spectra is often possible to evaluate the ratio of the various species (figure 19) since they have different chemical shift, in the case of the cyclic and acyclic forms at least.

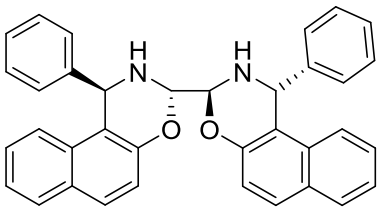


(figure 19)

Project

Taking as a reference a recent work[25] we decided to try to prepare the same ligand to properly characterize it and to check if the reported procedure was applicable to synthesize other analogues compounds starting from different aldehydes. The work cited above employed the racemic Betti base which was let to react with an aqueous 40% glyoxal solution in methanol. We tried the same reaction employing this time the enantiopure (*R*)-Betti [**1**] but it didn't lead to the expected and desired results because the precipitate isolated was a mixture of different species as confirmed by ^{1}H NMR. We tried different solvents, reaction conditions and starting materials (Betti base oxazinic derivative obtained from a dialdehyde mono-protected as an acetal) but we weren't successful; in every case just a really small amount of the suspected right product was isolable after column chromatography. After the observation that this target product showed a low solubility in THF we decided to exploit that performing the reaction in this solvent. Thus, in this manner, we hoped to be able to follow the reaction and to isolate the product by simple filtration.

The reaction performed in THF led to the obtainment of the desired product [**2**] as a white easily filterable precipitate that, otherwise, showed a trans,trans bis-oxazine structure (with a 5 % of cis,cis isomer) and not the bis-immine one as reported in the literature.[25,ii]



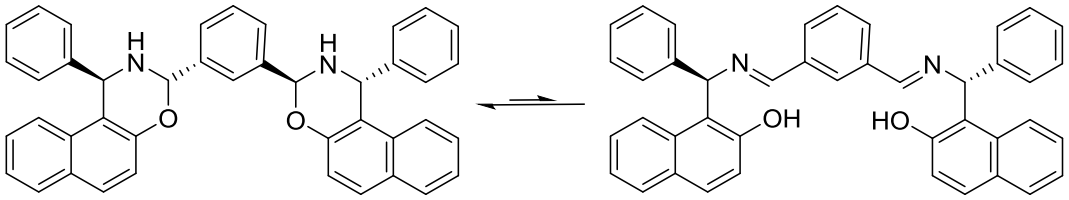
[**2**]

[ii] Indeed the NMR spectra reported in the latter were, in our opinion, not consistent with the bis-immine structure but, on the other hand reasonably consistent with the bis-oxazine one.

To evaluate if there were any differences due to the stereochemistry we tried to strictly follow the procedure of the work cited above employing the racemic Betti base but we weren't successful in obtaining the same results. The precipitate collected wasn't the hypothesized, desired product but, instead, a mixture of various species, as confirmed by 1H NMR spectroscopy.

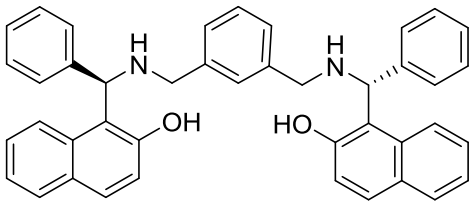
Subsequently we tried to synthesize a similar compound using the ortho-phthalaldehyde as the dialdehyde but the reaction, performed in various solvents, didn't lead to a single characterizable product neither after separation of the various products by flash chromatography (probably due to some possible intramolecular by-reactions).[14]

The employment of the isophthalaldehyde in methanol led instead to the precipitation of compound [**3**] as a white solid and in high yield. The observation of its ^{1}H and ^{13}C NMR spectra showed the presence of various species at the equilibrium: the cyclic trans,trans bis-oxazine [**3**] for the 53 %, the cis,cis isomers of the bis-oxazine for the 10 %, the acyclic bis-immine [**3b**] or a mono-immine-mono-oxazine form for the 11 % and other species not well identified for the remaining 26 %.



[**3**] [**3b**]

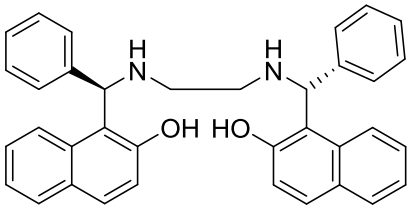
Anyway the obtainment of a single compound [**4**] from the reduction of precipitate [**3**] confirmed the hypothesis that all the supposed species were just isomers and tautomers, which gave the same expected acyclic product [**4**] upon reduction.



[**4**]

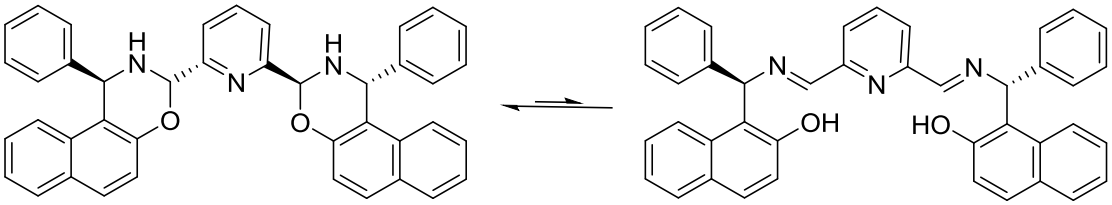
This was tried employing $LiAlH_4$ as the reducing agent but the desired product [**4**] was obtained just in low yield probably due to a Salan-type (figure 4) complexation of the product with the Al cation. Using $BH_3{\cdot}THF$, instead, it was observed a probable subsequent degradation of the reduced product. On the other hand, the employment of a 1 M dichloromethane solution of DIBALH (diisobutylaluminium hydride) as the reducing agent led to the obtainment of the product of interest in quantitative yield. The difficulty of performing the reaction with other reducing reactants apart DIBALH was observed

even with the compound [**5**] obtained from glyoxal, suggesting the necessary employment of this reagent for the reduction of similar compounds.



[**5**]

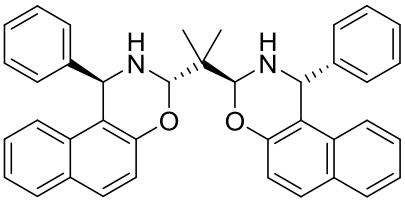
After the synthesis of compound [**3**] it was decided to prepare an analogue compound containing a heteroatom which could have worked as a further coordinating site for a Lewis acid. To achieve that a 2,6-pyridinedicarboxaldehyde, prepared from 2,6-pyridinedimethanol through Swern oxidation, was employed and the reaction, performed in methanol, quantitatively yielded compound [**6**] as a white solid isolated by filtration.



[**6**] [**6b**]

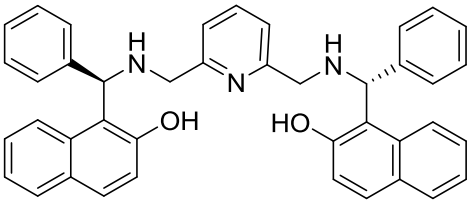
After observation of its NMR spectra, it was noted that the majority (90.6 %) of the compound existed in the trans,trans bis-oxazine form [**6**] while the acyclic bis-immine [**6b**] or the mono-immine-mono-oxazine form represented only the 7.0%. Furthermore the cis,cis isomers of the bis-oxazine were present just for the 2.4 % of the total.

To try to synthesize another similar compound, some crude 2,2-dimethylmalonaldehyde was obtained through Swern oxidation starting from 2,2-dimethylpropandiol. The attempts to isolate the dialdehyde were otherwise unsuccessful since it seemed that the latter polymerized quite easily. Thus, it was decided to let directly react the crude product and the (*R*)-Betti base in methanol; another time a white precipitate was isolated by simple filtration and it corresponded to the desired product [**7**] which existed in this case just in the trans,trans bis-oxazine form (with about 6 % of cis,cis isomers).

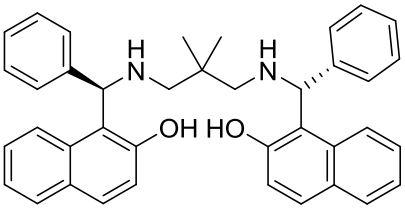


[**7**]

Even in these cases the use of DIBALH as the reducing agent led respectively to the desired acyclic products [**8**] and [**9**] in quantitative yield. Another time the supposition about which compound [**6**] consisted of species that were just isomers and tautomers was proven to be correct since only the expected product [**8**] was obtained upon reduction.



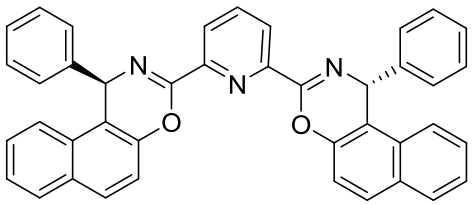
[**8**]



[**9**]

In the end, modifying the procedure of a recent publication,[26] it was tried a regioselective oxidation of the new formed oxazine ring to create a carbon-nitrogen double bond which involves the carbon between the two heteroatoms, without affecting the enantiopurity of the chiral centers. The oxidation worked in good yields to give a white precipitate, [**10**], only in the case of compound [**6**] and it was performed with $PhI(OAc)_2$ as the oxidizing agent, using methanol at room temperature as solvent. The reaction worked also in a mixture of THF and methanol, although some washings with THF were necessary to

obtain a pure product.[iii] In the case of compound [**3**] the reaction proceeded well in the same conditions but a byproduct was present even if with low percentage.

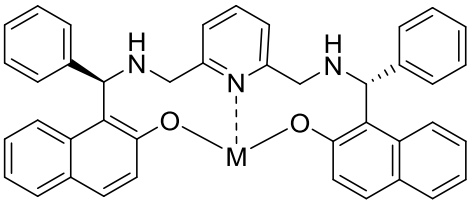


[**10**]

The synthesis of some Salan-type (figure 3) analogue complexes was tried starting from the various oxazines ([**2**], [**3**], [**6**] and [**7**]) but resulted unsuccessful despite the tries. This indicated that the iminic forms present at the equilibrium were not so reactive and that the latter was not so easily influenced by the presence of a Lewis acid. Furthermore, some acid catalyzed studies at the NMR have been carried out to investigate the equilibrium between oxazinic and imminic species since the latter are necessary for the formation of these hypothesized Salan-type analogues. Employing acetic acid it was observed only a scarce increase in imminic forms for both compounds [**3**] and [**6**] while for the ones present just as bis-oxazines ([**2**] and [**7**]) the amount of imminic forms was undetectable.

From the reduced compounds previously obtained ([**4**], [**5**], [**8**] and [**9**]) the subsequent synthesis of the respective metal complexes was tried under different conditions and employing different transition metal salts. Nevertheless it was possible to synthesize some of them only starting from compound [**8**]. Performing the reactions in EtOH as the solvent it was possible to obtain the complexes with Cu, Co, Mn, and Ni (figure 20). All the reactions occur immediately after the addition of the ligand solution to the metal salt one showing an intense coloration.

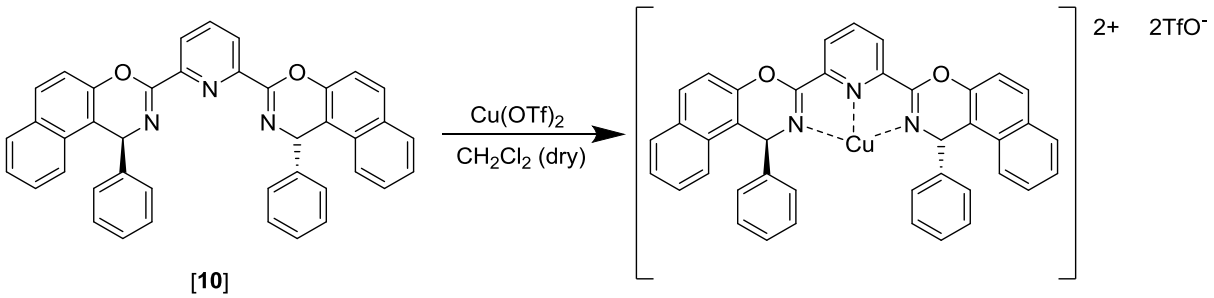
[iii] Furthermore it is important to notice that this product didn't seem stable under flash chromatography conditions because it tended to give another byproduct over time. After one night of stirring in a flask containing a silica suspension in dichloromethane it was indeed obtained the transformation of 2/3 of it into another product, which was hypothesized as the geometric isomer, with the carbon-nitrogen double bond involving the preexistent chiral center (probably the same analogue isomer was present as a byproduct in the oxidation of compound [**3**]).



(M = Mn, Co, Ni, Cu)

(figure 20)

On the other hand, the preparation of the active metal complex catalyst from the ligand [**10**] has always been performed under rigorous dry conditions (dry solvent, dry glassware and in the case of a subsequent asymmetric test reaction with some 3Å MS properly added); the formation of the catalyst Cu-[**10**] was confirmed by ES analysis (figure 21).



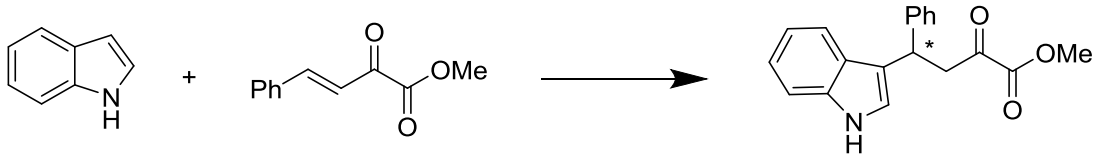
[**10**] Cu-[**10**]

(figure 21)

Test Reactions to determine the asymmetric induction

To test the previously prepared organometallic complexes as possible catalysts for asymmetric processes some organic reactions were performed and the enantiomeric excesses determined by HPLC with chiral columns.

The Friedel-Crafts reaction (even if it can be seen also as a Michael addition reaction) between the methyl-(*E*)-2-oxo-4-phenyl-3-butenoate and the indole has been investigated (figure 22).



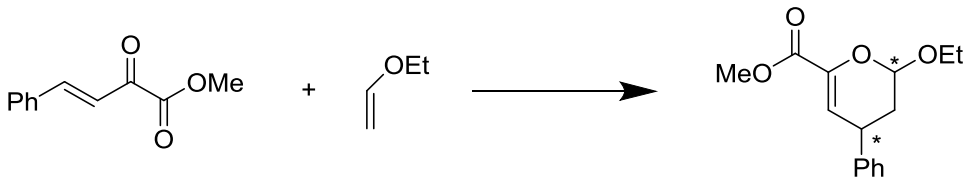
(figure 22)

The catalyst employed was a metal complex synthesized from $Cu(OTf)_2$ and the ligand [**10**]. This reaction was chosen because of the similarity of the ligand structure of [**10**] with the well-known bisoxazoline ligands,[27] which, after complexation with various metals, work as excellent enantioselective catalysts in these types of reactions, especially when a bidentate substrate is employed. The reactions were performed taking as a reference a procedure reported in literature[28] in which was used a Scandium-bisoxazoline complex. A screening of several dry solvents (THF, diethyl ether, toluene) was done but only dichloromethane gave an enantioenriched product in our case. The values of enantiomeric excess observed ranged from 30 to 63% showing a hardly understandable lack of reproducibility.

Subsequently the same reaction was performed employing an analogue catalyst derived from the same ligand and $Sc(OTf)_3$ but the value of ee was just up to 18%.

Furthermore another catalyst, $Cu(OAc)_2$-[**10**], was prepared using as the metal source dry $Cu(OAc)_2$ (confirmed by electron spray analysis) but it didn't give any enantioenriched product in the reaction studied.

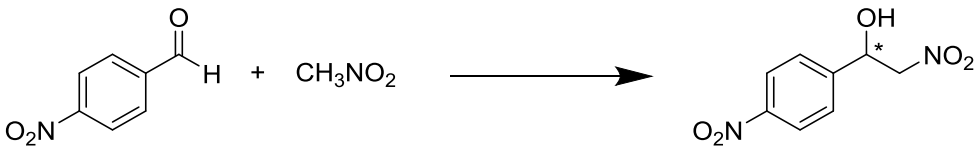
A Diels-Alder reaction between the methyl-(*E*)-2-oxo-4-phenyl-3-butenoate and the ethyl vinyl ether was also tested (figure 23), employing the same Cu-[**10**] catalyst in dichloromethane and following the procedure reported in literature.[29]



(figure 23)

In this case, carrying out the reaction at -30 °C, two diastereoisomers were obtained in a 75:25 ratio as determined by ^1H NMR. The enantiomeric excess of the first pair of enantiomers eluted at the chiral HPLC was between 30 and 70 %, while the second pair showed an enantiomeric excess between 0 and 40 %. Another time this was caused by a lack of reproducibility despite the tries.

Another asymmetric induction test was carried out on a Henry reaction, between *p*-nitrobenzaldehyde and nitromethane (figure 24).



(figure 24)

The use of two Cu-[**10**] catalysts, derived from $Cu(OAc)_2$ (solvent: EtOH, dry DCM) and from $Cu(OTf)_2$ (solvent: dry THF, dry DCM) respectively, didn't bring to any enantioenriched product. On the other hand when the reaction was performed employing a metal complex derived from the reduced ligand [**8**] some moderate values of enantiomeric excess were observed in some cases in EtOH. In the specific, the Mn complex gave an ee of about 5 %, the Cu complex gave an ee of about 10 % while the Ni complex gave an ee of about 20 %. Instead, the Co complex led to the obtainment of a racemate. All the reactions employing ligand [**8**] proceeded with a quantitative yield in 2 days at room temperature.

Conclusions

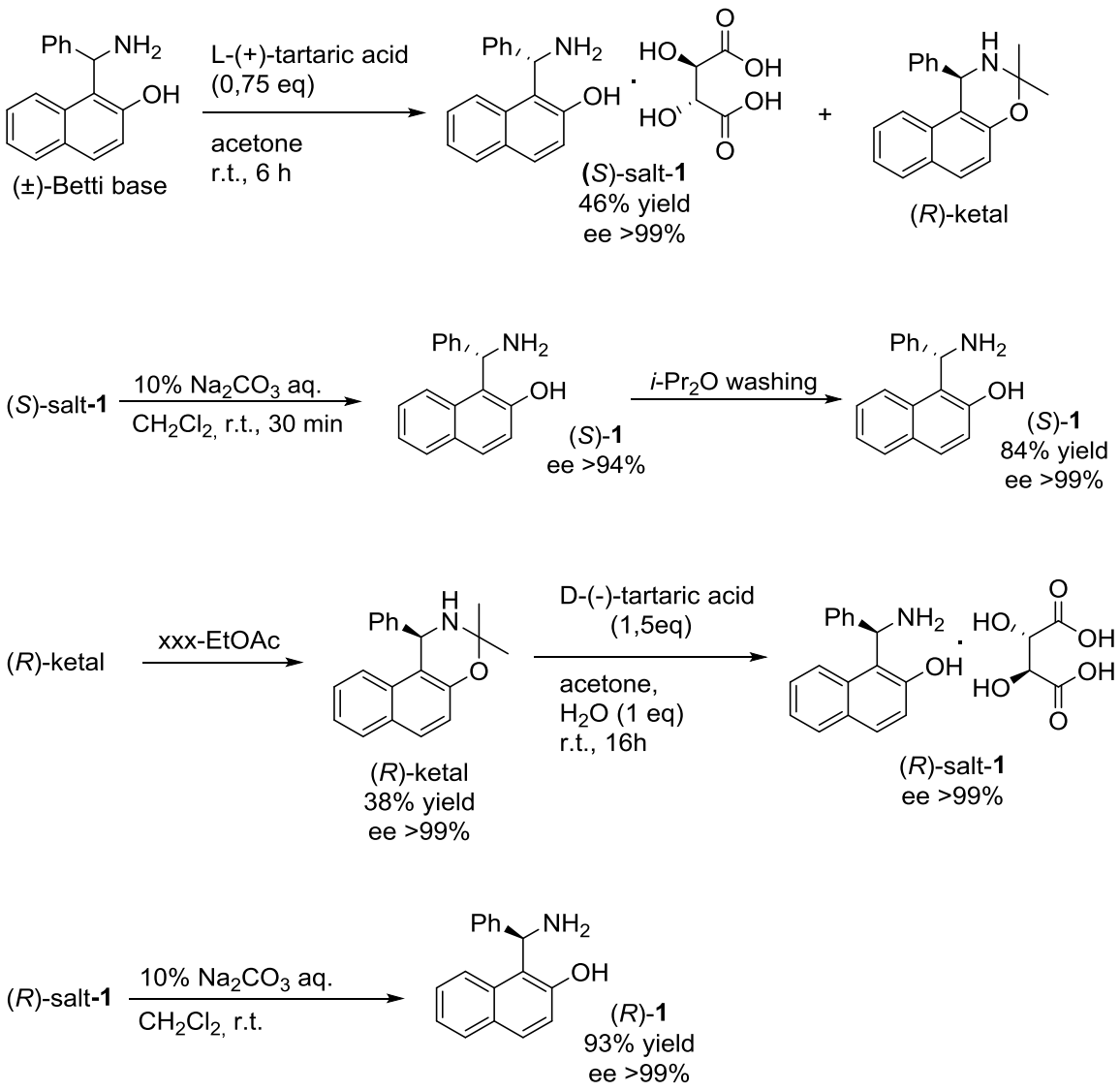
The synthesis of some novel enantiopure compounds (**[2]**, **[3]**, **[6]** and **[7]**) from *R*-(+)-Betti base and various dialdehydes was obtained. These compounds which were obtained in cyclic oxazinic forms were, in the case of compounds **[3]** and **[6]**, also present as open acyclic imine forms. Nevertheless the synthesis of some Salen-type analogues complexes was unsuccessful despite the tries. Some aminoalcohol (Salan-type) derivatives (**[4]**, **[5]**, **[8]**, **[9]**) of these compounds were obtained upon reduction and employing compound **[8]** was possible to obtain various metal complexes (**Ni-[8]**, **Mn-[8]**, **Co-[8]** and **Cu-[8]**) showing that **[8]** behaves as an efficient ligand for transition metals. On the other hand the mild oxidation of **[6]** led to the obtainment of compound **[10]**, a novel 6-membered analogue bisoxazoline ligand, from which **Cu-[10]** and **$Cu(OAc)_2$-[10]** complexes were prepared. The metal complexes were employed in some reactions to test the asymmetric induction, which was in some cases up to discrete values.

Experimental part

Reagents and Instrumentation employed

TLC, silica gel plates 60F254 (Fluka)
HPLC-DAD, *Hewlett Packard 1100* instrument with chiral columns
Perkin Elmer 341 polarimeter for the determination of the optical activity.
dr are the diastereoisomeric excesses
ee are the enantiomeric excesses
DCM: dichloromethane (dried through distillation over CaH_2)
THF: tetrahydrofuran (dried through distillation over metallic Na)
DMSO: dimethylsulfoxide (dried through distillation over CaH_2)
DIBALH: diisobutylaluminium hydride
IBD: $PhI(OAc)_2$ (recrystallized from AcOH)
MS: molecular sieves
^1H and ^{13}C NMR spectra were recorded (if not differently specified) at 600 and 150 MHz respectively, using $CDCl_3$ as the solvent and are reported in ppm downfield from TMS ($\delta = 0$) for ^1H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.00$) for ^{13}C NMR. The enantiomeric excess (ee) of the products were determined by HPLC using a Daicel Chiralpak AD-H column, a Chiralcel OD-H column, a Chiralcel OJ-H column or a Chiralpak IC column).

Resolution of a racemic mixture of the Betti base [1][8]



As first operation the acetone was dried over drierite (dry $CaSO_4$, around 25g/L of acetone) letting stir the suspension for several hours at room temperature. After that, the acetone was separated through decantation, some fresh drierite was added (10g/L) and, after one hour under reflux, hence distilled.

To a racemic Betti base solution in dry acetone (200 mmol in 200 mL of solvent) was added under stirring a solution of L-(+)-tartaric acid (22.6 g, 150 mmol) dissolved in 800 mL of acetone. The mixture was let react under stirring and with a $CaCl_2$ trap for 16 hours.

Thus, the precipitate was isolated by filtration on a Büchner funnel and washed with acetone, obtaining 36.5 g (91.4 mmol) of (*S*)-salt-1. The latter was hence suspended in

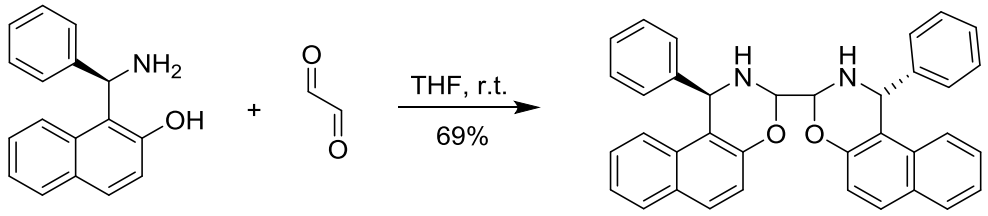
175 mL of DCM and, after cooling of it to 0 °C, 30 mL of a 10% aqueous solution of Na_2CO_3 were added. The stirring was continued until the suspended solid disappeared. Then, in a separation funnel, the aqueous layer was separated and extracted with 50 mL of DCM. The reunited organic phases were washed with 50 mL of water and 50 mL of a saturated solution of NaCl, hence, dried over Na_2SO_4, filtered and the solvent rotavaporated to obtain 22.2 g (89.0 mmol) of Betti base with an er = 97/3. In the end the product was suspended in 300 mL of boiling *i*-Pr_2O and, after cooling, 20.8 g (83.4 mmol) of (*S*)-1 with an er > 99.5/0.5 were obtained as a white solid (overall yield 42%). The enantiomeric purity of it was determined by ^{1}H NMR, employing an enantiopure auxiliary as described in literature.[6]

To the acetone solution obtained from the first filtration and containing the (*R*)-ketal the acetone used to wash the (*S*)-salt-**1** was added, hence 20 mL of a saturated aqueous solution of Na_2CO_3 were added. After removal of almost all the acetone present, 200 mL of DCM and 200 mL of water were added to the residue. The aqueous layer was separated and extracted with 50 mL of DCM. Thus the reunited organic phases were washed with water, brine and dried over Na_2SO_4. After removal of the solvent at the rotavapor and at the high vacuum pump, 24.5 g (84.7 mmol) of residue were recrystallized from 100 mL of EtOAc to obtain 22.0 g (76.0 mmol) of (*R*)-ketal compound with an ee > 99.5%, which was determined by HPLC.

At this point the (*R*)-*N*,*O*-ketal (76.0 mmol) was dissolved in 115 mL of dry acetone in a dried round-bottom flask with a $CaCl_2$ protecting valve and, in sequence, 17 g (113 mmol) of D-(-)-tartaric acid, 300 mL of acetone and 1.4 mL (76 mmol) of water were added. The resulting suspension was let to react overnight and then filtered on a Büchner funnel, washing with acetone, to obtain the (*R*)-salt-1 as a white solid. From the latter, 17.6 g (70.6 mmol) of (*R*)-1 were obtained operating as previously described for its enantiomer (overall yield 35 %).

Synthesis of compound [2]

(1*R*,1'*R*)-1,1'-Diphenyl-2,2',3,3'-tetrahydro-1*H*,1'*H*-3,3'-binaphtho[1,2-*e*][1,3]oxazine



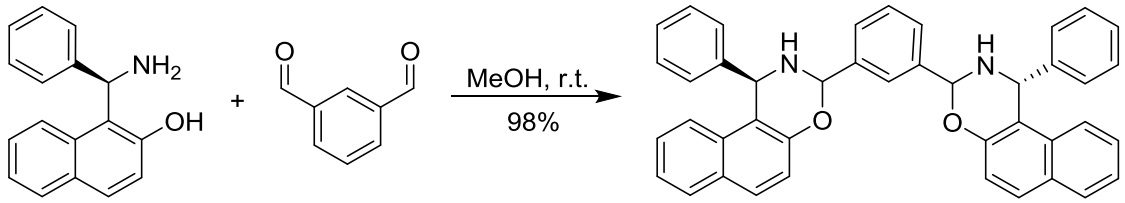
R-(+)-Betti [**1**] [**2**]

To a stirred solution of (*R*)-Betti [**1**], prepared dissolving 502.3 mg (2.015 mmol) in 2 mL of dry THF, 115 µL (1 mmol) of glyoxal (40% aqueous solution) diluted in 1.5 mL of dry THF were added. After around 4 days the resulting precipitate was filtered on a Büchner funnel to obtain 362 mg of product [**2**] (yield = 69%).

$[\alpha]^{24}_{D}$ = -2.63° (c = 0.935 g/mL; $CHCl_3$); ^{1}H NMR δ 7.77-7.70 (m, 4H), 7.33-7.13 (m, 18H), 5.61 (s, 2H), 4.81 (s, 2H), 3.49 (bs, 2H); ^{13}C NMR δ 151.8, 142.3, 131.4, 129.3, 129.2, 128.8, 128.44, 128.36, 127.4, 126.6, 123.3, 122.8, 119.1, 114.4, 81.1, 53.4

Synthesis of compound [3]

1,3-bis((1*R*)-1-Phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazin-3-yl)benzene



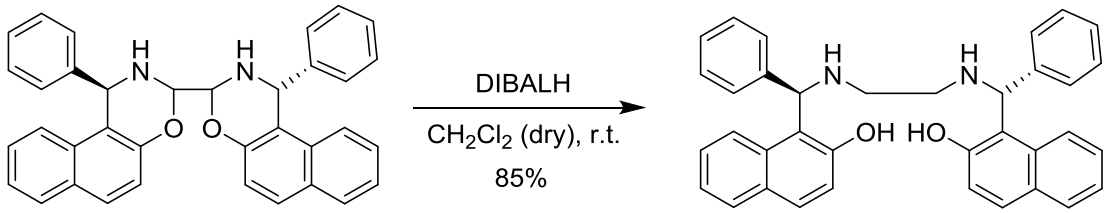
R-(+)-Betti [**1**] [**3**]

501 mg (2.01 mmol) of (*R*)-Betti [**1**] were dissolved in 35 mL of MeOH using an ultrasonic bath. Then 133 mg (0.992 mmol) of isophthalaldehyde in 5 mL of MeOH were added to the stirred solution of (*R*)-Betti. Thus, after around 38 hours, the resulting suspension was filtered on a Büchner funnel to yield 578 mg of the precipitated product [**3**] (yield = 98%).

$[\alpha]^{24}_{D}$ = -211° (c = 0.975 g/mL; $CHCl_3$); ^{1}H NMR diagnostic signals for the trans bis-oxazine (main product) δ 5.70 (s, 2H), 5.67 (s, 2H); ^{1}H NMR diagnostic signals for the cis bis-oxazine isomers δ 5.95 (s, 2H), 5.84 (bs, 2H); ^{1}H NMR diagnostic signals for the bis-immine/mono-immine-mono-oxazine δ 8.64 (s, 2H), 6.45 (s, 2H); ^{13}C NMR diagnostic signals for the trans bis-oxazine (main product) δ 82.4, 53.9; ^{13}C NMR diagnostic signals for the cis bis-oxazine isomers δ 86.6, 57.6; ^{13}C NMR diagnostic signals for the bis-immine/mono-immine-mono-oxazine δ 161.8, 74.7 (determined after HSQC NMR experiment).

Reduction of compound [2] to compound [5]

1,1'-((1*R*,1'*R*)-(Ethane-1,2-diylbis(azanediyl))bis(phenylmethylene))bis(naphthalen-2-ol)



[**2**] [**5**]

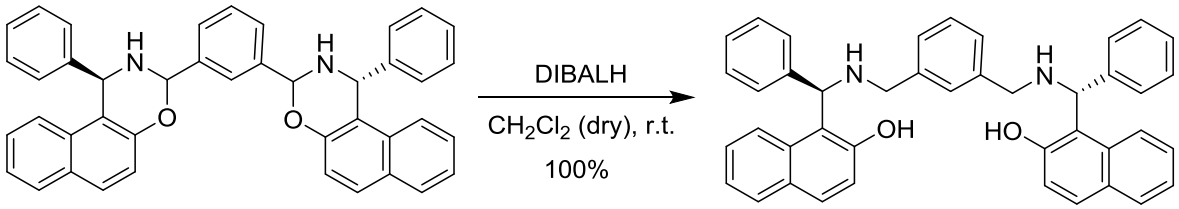
0.7 mL (0.7 mmol) of a 1 M DIBALH solution in CH_2Cl_2 were placed in a dried three-neck round-bottom flask fitted with a thermometer and under nitrogen flow. Then 62.0 mg (0.119 mmol) of [**2**] dissolved in 4 mL of dry CH_2Cl_2 were added dropwise through a rubber septum. During the addition a little increment of temperature, from 17 to 21 °C, was observed. The reaction was quenched after 5 hours with some drops of MeOH and 0,5 mL of a saturated solution of NH_4Cl. After 30 minutes of stirring the initial gel formed returned liquid and the organic layer separated from the aqueous one through decantation. The latter was thus extracted three times with DCM until any traces of the product was detectable by TLC. The reunited organic phases were dried over $MgSO_4$ to obtain 58 mg of crude product. After flash chromatography were collected 53 mg of product [**5**] (yield = 85%).

$[\alpha]^{24}_{D}$ = -204° (c = 0.745 g/mL; $CHCl_3$); ^{1}H NMR δ 7.73-7.64 (m, 6H), 7.43 (m, 4H), 7.32-7.20 (m, 10H), 7.13 (d, *J* = 8.9 Hz, 2H), 5.64 (s, 2H), 3.01 (m, 4H), 1.26 (bs, 2H);

^{13}C NMR δ 156.3, 140.9, 132.5, 129.9, 129.1, 128.8, 128.7, 128.2, 127.7, 126.6, 122.6, 121.1, 120.0, 113.3, 63.8, 47.9

Reduction of compound [3] to compound [4]

1,1'-((1*R*,1'*R*)-((1,3-Phenylenebis(methylene))bis(azanediyl))bis(phenylmethylene))bis(naphthalen-2-ol)

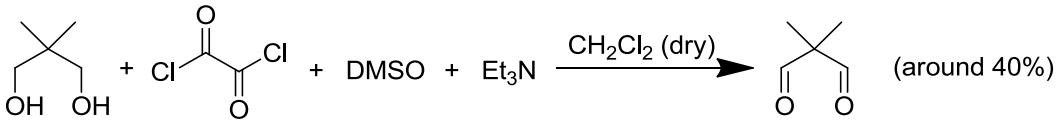


[**3**] [**4**]

In a 50 mL dried three-neck round bottom flask fitted with a thermometer and under nitrogen flow 7 mL (7 mmol) of a 1 M DIBALH solution in CH_2Cl_2 were placed. Then 991 mg (1.66 mmol) of [**3**] dissolved in 18 mL of dry CH_2Cl_2 were added dropwise maintaining the temperature between 0 and 5 °C with the use of an ice-water bath. The reaction was let stir overnight at room temperature hence quenched with some drops of MeOH and 10 mL of a saturated aqueous solution of NH_4Cl. The initial gel formed was stirred for 2 hours obtaining again a solution and the organic layer separated through decantation, thus, the aqueous phase extracted with DCM until any traces of the product was detectable by TLC. The reunited organic phases were dried over $MgSO_4$ and filtered. Then, after flash chromatography on silica gel 997 mg (1.66 mmol) of product [**4**] were obtained (yield = 100%).

$[\alpha]^{24}_{D}$ = -2.28° (c = 0. 500 g/mL; $CHCl_3$); ^{1}H NMR δ 13.42 (bs, 2H), 7.73 (d, *J* = 8.8 Hz, 4H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.40-7.34 (m, 5H), 7.29-7.14 (m, 15H), 5.73 (s, 2H), 4.02 and 3.81 (AB-system, *J* = 13.2 Hz, 4H), 2.25 (bs, 2H); ^{13}C NMR δ 156.7, 141.1, 138.4, 132.6, 129.9, 129.3, 129.1, 128.9 (2C), 128.7, 128.14, 128.08, 127.8, 126.5, 122.5, 121.1, 120.1, 112.9, 62.8, 52.5

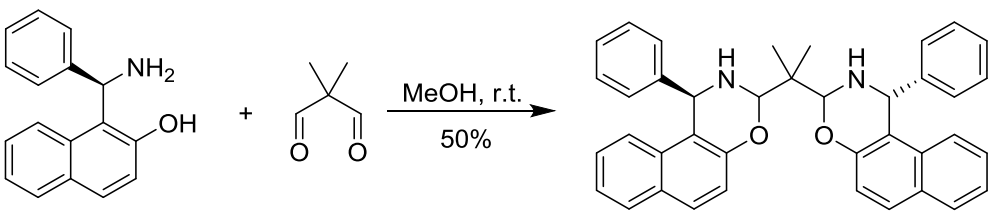
Synthesis of 2,2-dimethylmalonaldehyde



In a 250 mL dried four-neck round bottom flask 4.1 mL (48 mmol) of oxalyl chloride diluted in 70 mL of dry CH_2Cl_2 were placed and, at -78 °C, a solution of DMSO (7 mL, 98 mmol) in dry CH_2Cl_2 (14mL) was added dropwise in 20 minutes and maintaining the temperature between -78 and -68 °C. After stirring for 30 minutes 2 g (19.2 mmol) of 2,2-dimethyl-1,3-propandiol, dissolved in 22 mL of dry CH_2Cl_2 with the use of an ultrasonic bath, were added to the reaction mixture at -78 °C. After 90 minutes of stirring, 21 mL (151 mmol) of Et_3N were added (temperature between -78 and -67 °C). Then the temperature of -78 °C was maintained for 30 minutes, thus the reaction mixture was stirred for further 3 hours at room temperature and, in the end, quenched with 25 mL of a saturated solution of NH_4Cl. The aqueous phase extracted three times with 5 mL of CH_2Cl_2. The reunited organic phases were washed with 45 mL of HCl 1N until neutral pH, dried over Na_2SO_4, filtered and rotavaporated (at a temperature below 20 °C) to obtain 2.194 g of crude product. ^{1}H NMR (300 MHz) δ 9.63 (s, 2H), 1.36 (s, 6H).
The crude, containing DMSO and some byproducts, was utilized without further purification in the next reactions.

Synthesis of compound [7]

(1*R*,1'*R*)-3,3'-(Propane-2,2-diyl)bis(1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine)



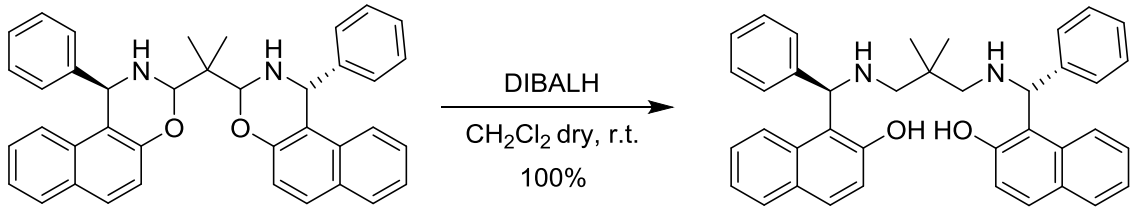
R-(+)-Betti [**1**] [**7**]

133 mg (0.533 mmol) of (*R*)-Betti [**1**] dissolved in 10 mL of MeOH were placed in a 25 mL round-bottom flask and subsequently 80 mg of crude 2,2-dimethylmalonaldehyde in 4 mL of MeOH were added. After around 45 minutes a white precipitate was formed from the reaction solution, thus, 24 hours later, filtered on a Büchner funnel to obtain 72.0 mg (0.128 mmol) of product [**7**] (yield around 50% calculated in relation with the amount of the (*R*)-Betti).

$[\alpha]^{24}_{D}$ = +18.8° (c = 0.910 g/mL; $CHCl_3$); ^{1}H NMR δ 7.75 (m, 2H), 7.62 (d, J = 9.0 Hz, 2H), 7.37 (m, 2H), 7.30-7.20 (m, 5H), 7.13 (m, 4H), 7.00-6.93 (m, 5H), 6.82 (d, J = 9.0 Hz, 2H), 5.53 (s, 2H), 4.58 (s, 2H), 3.46 (bs, 2H); ^{13}C NMR δ 152.6, 142.2, 131.8, 128.9, 128.7, 128.5, 128.4, 127.9, 126.9, 126.3, 122.9, 122.7, 119.5, 114.5, 86.2, 53.3, 40.5, 20.2

Reduction of compound [7] to compound [9]

1,1'-((1*R*,1'*R*)-((2,2-Dimethylpropane-1,3-diyl)bis(azanediyl))bis(phenylmethylene))bis(naphthalen-2-ol)

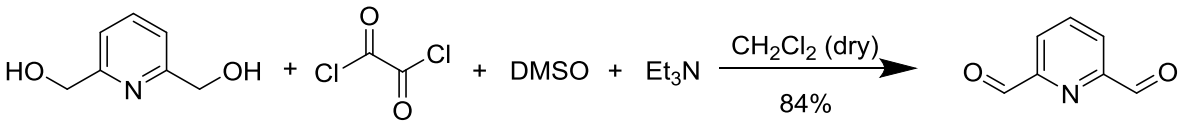


[**7**] [**9**]

In a dried three-neck round bottom flask fitted with a thermometer and under nitrogen flow were placed 1.5 mL (1.5 mmol) of a 1 M DIBALH solution in CH_2Cl_2. Then 207 mg (0.368 mmol) of [**7**], dissolved in 4 mL of dry CH_2Cl_2, were added dropwise maintaining the temperature between 0 and 5 °C with the use of an ice-water bath. The reaction mixture was let stir at room temperature and resulted complete after 1 hour, hence quenched with some drops of MeOH and 2 mL of a saturated aqueous solution of NH_4Cl. The initial gel formed was stirred for 1 hour obtaining again a solution and the organic layer separated through decantation, thus, the aqueous phase extracted with DCM until any traces of the product was detectable by TLC. The reunited organic phases

were dried over $MgSO_4$ and filtered. Then, after flash chromatography on silica gel 208 mg (0.368 mmol) of product [**9**] were obtained (yield = 100%).
$[\alpha]^{rt}_D$ = -2.101 (c = 0.810 g/mL; $CHCl_3$); ^{1}H NMR δ 13.05 (bs, 2H), 7.77 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J*= 8.0 Hz, 2H), 7.65 (d, *J* = 9.0 Hz, 2H), 7.45 (m, 4H), 7.36 (m, 2H), 7.28-7.21 (m, 8H), 7.05 (d, *J* = 8.9 Hz, 2H), 5.65 (s, 2H), 2.68 and 2.65 (AB-system, *J* = 11.9 Hz, 4H), 1.57 (bs, 2H), 1.03 (s, 6H); ^{13}C NMR δ 156.0, 141.0, 132.4, 129.8, 129.1, 128.8, 128.6, 128.2, 127.8, 126.5, 122.5, 121.1, 119.9, 114.0, 64.6, 57.9, 34.6, 24.5

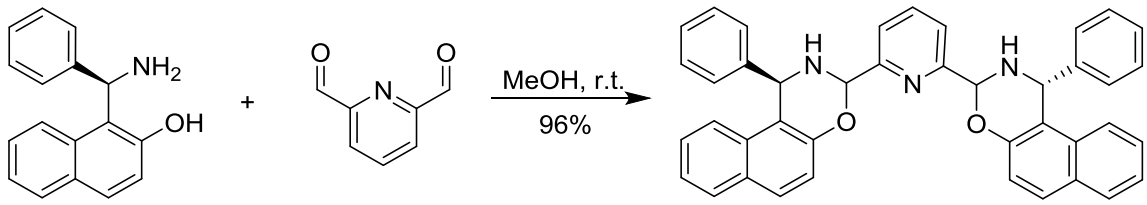
Synthesis of 2,6-pyridinedicarboxaldehyde[30]



In a 100 mL dried four-neck round bottom flask were placed 22.5 mL of dry CH_2Cl_2, 1.4 mL (16.5 mmol) of oxalyl chloride and, at -78 °C, a solution of DMSO (3 mL, 42.2 mmol) in dry CH_2Cl_2 (4.5 mL) was added dropwise maintaining the temperature below -70 °C (gas evolution for the first third of the addition). After stirring for some minutes at -78 °C the reaction mixture was stirred for 5 minutes at -50 °C and cooled again at -78°C. Then 762 mg (5.48 mmol) of 2,6-pyridine dimethanol, dissolved in 3 mL (42.2 mmol) of DMSO and 4.5 mL of dry CH_2Cl_2, were added dropwise to the reaction mixture maintaining the temperature between -78 and -70 °C. After stirring 45 minutes at -78 °C, with the contemporary formation of a white precipitate, the resulting suspension was stirred some minutes at -50 °C, thus cooled again to -78 °C. Subsequently 7 mL (50.2 mmol) of Et_3N were added maintaining the temperature below -70 °C and resulting in the formation of a gel, then let warm until room temperature, thus stirred another 2 hours. After the addition of 40 mL of water a solution was obtained again. The organic layer separated and the aqueous one extracted three times with 25 mL of DCM. The reunited organic phases were washed three times with 25 mL of a saturated solution of NaCl, dried over $MgSO_4$ and filtered on celite. After flash chromatography 623 mg (4.61 mmol) of product was obtained (yield = 84%). ^{1}H NMR (300 MHz) δ 10.18 (d, *J* = 0.8 Hz, 2H), 8.21-8.17 (m, 2H), 8.13-8.06 (m, 1H); ^{13}C NMR in agreement with the one reported in literature.[30]

Synthesis of compound [6]

2,6-bis((1*R*)-1-Phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazin-3-yl)pyridine



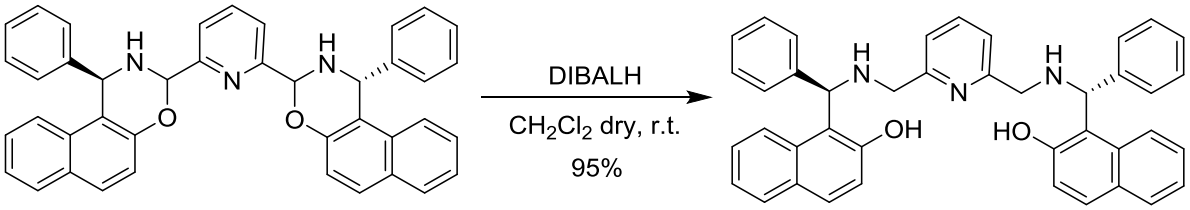
R-(+)-Betti [**1**] [**6**]

1.984 g (7.958 mmol) of (*R*)-Betti [**1**] were dissolved in 120 mL of MeOH with the aid of an ultrasonic bath, then 536.1 mg (3.968 mmol) of 2,6-pyridinedicarboxaldehyde dissolved in 45 mL of MeOH were added. After stirring for 38 hours the resulting suspension was filtered on a Büchner funnel to obtain 2.276 g (3.808 mmol) of [**6**] as a white solid (yield = 96%).

$[\alpha]^{24}_{D}$ = -293° (c = 0.970 g/mL; $CHCl_3$); ^{1}H NMR diagnostic signals for the trans bis-oxazine (main product) δ 7.78-7.74 (m, 3H), 7.73 (d, J = 8.9 Hz, 2H), 7.41 (d, J = 7.6 Hz, 2H), 7.40-7.24 (m, 16H), 7.12 (d, J = 9.1 Hz, 2H), 5.75 (s, 2H), 5.70 (s, 2H), 3.69 (bs, 2H); ^{13}C NMR diagnostic signals for the trans bis-oxazine (main product) δ 156.0, 152.4, 142.6, 137.8, 131.5, 129.2, 129.1, 128.8, 128.4, 128.3, 127.3, 126.5, 123.2, 122.9, 122.6, 119.2, 114.0, 82.7, 53.4; ^{1}H NMR diagnostic signals for the bis-immine or the mono-immine-mono-oxazine δ 11.24 (s, 2H, -OH), 8.77 (s, 2H, -N=CH-), 6.51 (s, 2H, -CH-benzylic); ^{1}H NMR diagnostic signals for the cis isomers of the bis-oxazine δ 5.96 (m, 2H), 5.89 (m, 2H).

Reduction of compound [6] to compound [8]

1,1'-((1*R*,1'*R*)-((Pyridine-2,6-diylbis(methylene))bis(azanediyl))bis(phenylmethylene))bis(naphthalen-2-ol)

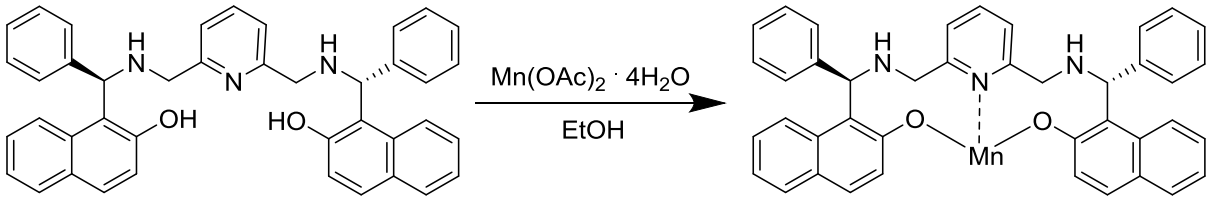


[**6**] [**8**]

In a 50 mL dried three-neck round bottom flask fitted with a thermometer and under nitrogen flow were placed 7 mL (7 mmol) of a 1 M DIBALH solution in CH_2Cl_2. Then 996 mg (1.67 mmol) of [**6**] dissolved in 20 mL of dry CH_2Cl_2 were added dropwise keeping the temperature between 0 and 7 °C with the use of an ice-water bath. The reaction mixture was let stir at room temperature and resulted complete after 2 hours, hence quenched with some drops of MeOH and 10 mL of a saturated solution of NH_4Cl. The initial gel formed was stirred for 2 hours obtaining again a solution and the organic layer separated through decantation, thus, the aqueous phase extracted with DCM until any traces of the product was detectable by TLC. The reunited organic phases were dried over $MgSO_4$ and filtered. Then, after flash chromatography on silica gel 953 (1.58 mmol) mg of product [**8**] were obtained (yield = 95%).

$[\alpha]^{24}_{D}$ = -1.18° (c = 1.195 g/mL; $CHCl_3$); ^{1}H NMR δ 13.55 (bs, 2H), 7.74 (d, J = 8.8 Hz, 4H), 7.61-7.57 (m, 3H), 7.37-7.34 (m, 4H), 7.30 (m, 2H), 7.25-7.18 (m, 10H), 7.08 (d, J = 7.6 Hz, 2H), 5.68 (s, 2H), 4.12 and 4.00 (AB-system, J = 14.2 Hz, 4H), 3.30 (bs, 2H); ^{13}C NMR δ 157.1, 156.8, 141.0, 137.4, 132.7, 129.8, 129.0, 128.8, 128.7, 128.1, 127.7, 126.5, 122.5, 121.9, 121.1, 120.1, 113.1, 63.0, 53.0

Preparation of the complex Mn-[8]

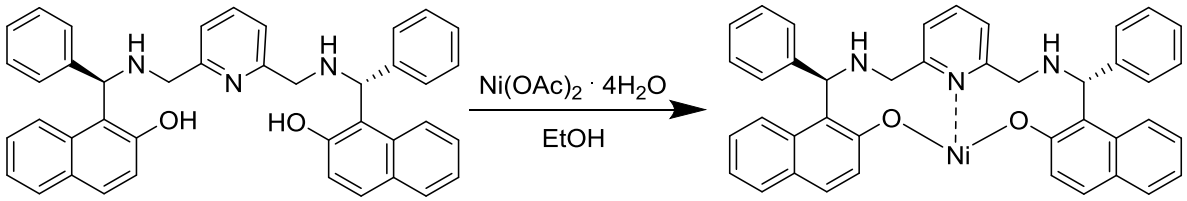


[**8**] Mn-[**8**]

7.7 mg (0.013 mmol) of [**8**] were dissolved in 5 mL of EtOH by the aid of an ultrasonic bath and subsequently added to a solution of 5.1 mg (0.021 mmol) of $Mn(OAc)_2 \cdot 4\ H_2O$ dissolved in 2 mL of EtOH. Immediately after the addition of the ligand the resulting solution turned to dark green. The reaction resulted complete by TLC showing an absence of ligand. Furthermore the product was confirmed by electron spray analysis with positive ions.

Mass (TOF ES+) = m/z 654 $(M)^+$

Preparation of the complex Ni-[8]

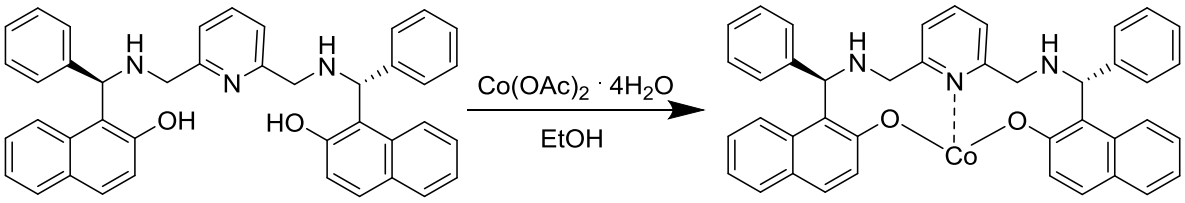


[**8**] Ni-[**8**]

7.2 mg (0.012 mmol) of [**8**] were dissolved in 2.5 mL of EtOH by the aid of an ultrasonic bath and subsequently added to a solution of 3.5 mg (0.014 mmol) of $Ni(OAc)_2 \cdot 4\ H_2O$ dissolved in 2 mL of EtOH. Immediately after the addition of the ligand the resulting solution turned to yellow. The reaction resulted complete by TLC showing an absence of ligand. Furthermore the product was confirmed by electron spray analysis with positive ions.

Mass (TOF ES+) = m/z 658 $(M + 1)^+$

Preparation of the complex Co-[8]

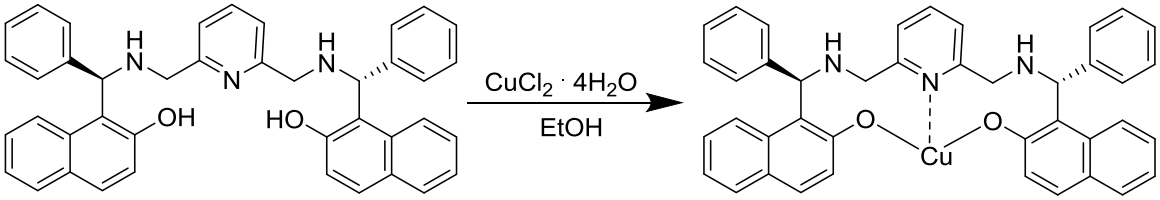


[**8**] Co-[**8**]

6.0 mg (0.010 mmol) of [**8**] were dissolved in 5 mL of EtOH by the aid of an ultrasonic bath and subsequently added to a pink solution of 4.2 mg (0.017 mmol) of $Co(OAc)_2 \cdot 4 H_2O$ dissolved in 2 mL of EtOH. Immediately after the addition of the ligand the resulting solution turned to dark green. The reaction resulted complete by TLC showing an absence of ligand. Furthermore the product was confirmed by electron spray analysis with positive ions.

Mass (TOF ES+) = m/z 658 $(M)^+$

Preparation of the complex Cu-[8]

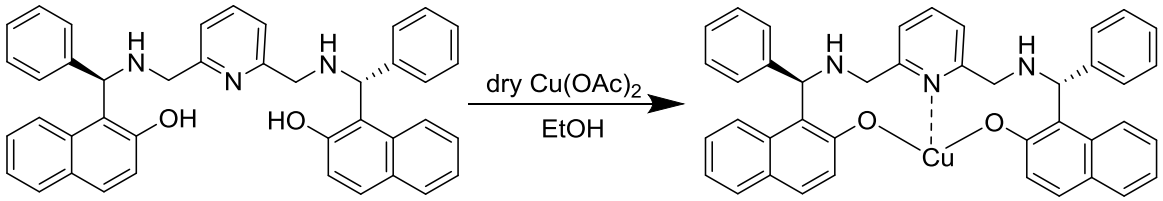


[**8**] Cu-[**8**]

6.0 mg (0.010 mmol) of [**8**] were dissolved in 5 mL of EtOH by the aid of an ultrasonic bath and subsequently added to a light green solution of 2.5 mg (0.015 mmol) of $CuCl_2 \cdot 4 H_2O$ dissolved in 2 mL of EtOH. Immediately after the addition of the ligand the resulting solution turned to dark green. The reaction resulted complete by TLC showing an absence of ligand. Furthermore the product was confirmed by electron spray analysis with positive ions.

Mass (TOF ES+) = m/z 663 $(M + 1)^+$

Preparation of the complex Cu-[8]



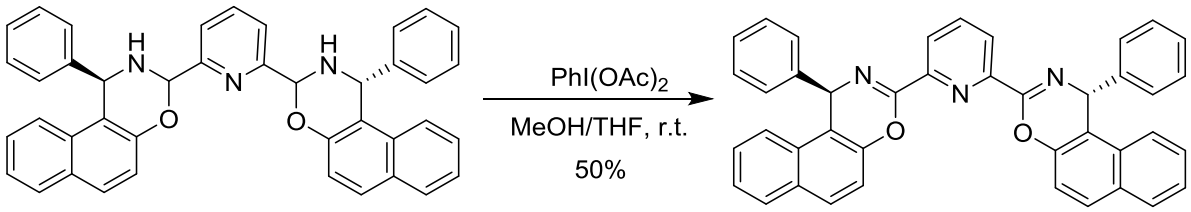
[**8**] Cu-[**8**]

2.0 mg (0.0083 mmol) of dry $Cu(OAc)_2$ and 5.0 mg (0.084 mmol) of [**8**] were weighted in a 2 mL vial to which 1 mL of EtOH was added. After some minutes it was observed a complete dissolution of both the metal salt and the ligand leading to a dark green solution. The ligand resulted absent by TLC and the formation of the product was confirmed by electron spray analysis with positive ions.

Mass (TOF ES+) = m/z 663 $(M + 1)^+$

Oxidation of compound [6] to compound [10]

2,6-bis((*R*)-1-Phenyl-1*H*-naphtho[1,2-*e*][1,3]oxazin-3-yl)pyridine



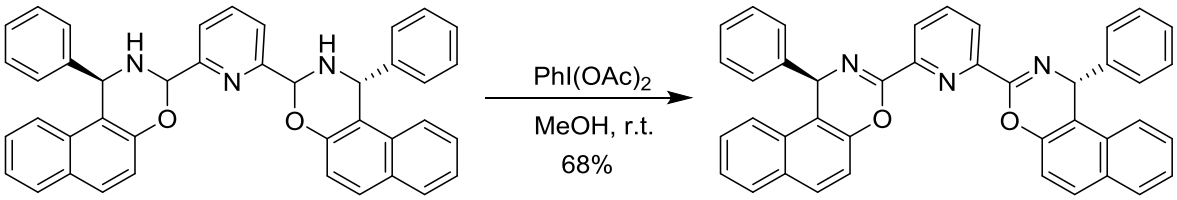
[**6**] [**10**]

207.2 mg (0.3467 mmol) of [**6**] were dissolved in 11 mL of THF and the resulting solution was added in a 100 mL round-bottom flask containing 248.2 mg (0.7706 mmol) of $PhI(OAc)_2$ which were previously dissolved in 55 mL of MeOH. After 5 minutes the solution turned towards a yellow/green color and 15 hours later it was rotavaporated, redissolved in THF and filtered on paper at around 50 °C, then cooled to obtain a precipitation of a white solid, filtered on a Büchner funnel and washed several times with THF to obtain 102.2 mg (0.1721 mmol) of [**10**] (yield = 50 %).

$[\alpha]^{24}_{D}$ = +91.3° (c = 0.790 g/mL; $CHCl_3$); ^{1}H NMR δ 8.27 (d, *J* = 7.9 Hz, 2H), 7.87 (d, *J* = 9.1 Hz, 2H), 7.83-7.79 (m, 3H), 7.68 (m, 2H), 7.57 (d, *J* = 8.9 Hz, 2H), 7.42 (m, 4H), 7.39 (m, 4H), 7.27 (m, 4H), 7.19 (m, 2H), 6.53 (s, 2H); ^{13}C NMR δ 150.0, 149.8, 146.8, 143.2, 137.3, 131.6, 130.0, 129.4, 128.8, 128.6, 128.1, 127.6, 127.0, 125.2, 124.9, 123.2, 117.1, 113.4, 57.4

Oxidation of compound [6] to compound [10]

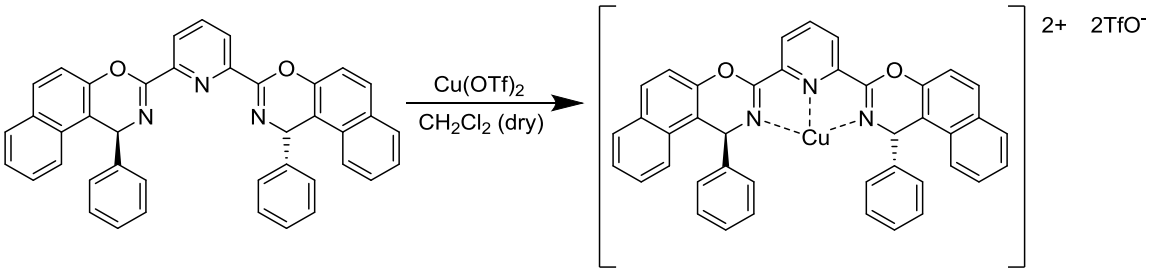
2,6-bis((*R*)-1-Phenyl-1*H*-naphtho[1,2-*e*][1,3]oxazin-3-yl)pyridine



[**6**] [**10**]

230 mg (0.714 mmol) of $PhI(OAc)_2$ were added to a suspension of 203 mg (0.340 mmol) of [**6**] in 30 mL of MeOH. After 2 hours the reaction resulted complete by TLC and thus the suspension was filtered on a Büchner funnel to obtain 138 mg (0.232 mmol) of [**10**] as a white solid (yield = 68%).

Preparation of the complex Cu-[10]



[**10**] Cu-[**10**]

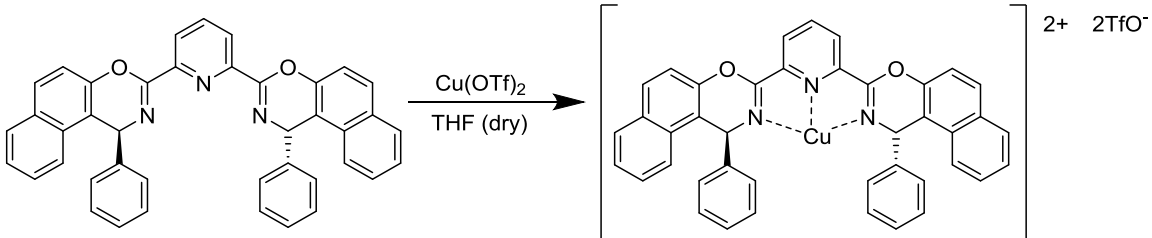
In a 5 mL dried round-bottom flask 7.3 mg (0.012 mmol) of [**10**] dissolved in 1 mL of dry CH_2Cl_2 were added to 7.0 mg (0.019 mmol) of $Cu(OTf)_2$ suspended in 1 mL of dry CH_2Cl_2. Immediately was observed an intense yellow coloration of the solution which

turned to green after two hours with complete dissolution of the copper salt. The absence of the free ligand was observed by TLC and the product formation was confirmed by electron spray analysis with positive ions ($MM_{product\ (calculated)}$ = 954 g/mol).

Mass (TOF ES+) = m/z 977 $(M + Na)^+$

Mass (TOF ES+) = m/z 805 $(M - OTf)^+$

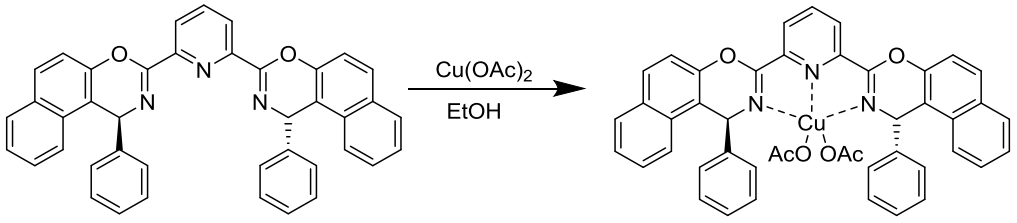
Preparation of the complex Cu-[10]



[**10**] Cu-[**10**]

In a 5 mL dried round-bottom flask 4.9 mg (0.008 mmol) of [**10**] dissolved in 1 mL of dry THF were added to 4.7 mg (0.013 mmol) of $Cu(OTf)_2$ dissolved in 0.5 mL of dry THF. Immediately the color of the solution turned from colorless into an intense light green. The absence of the free ligand was observed by TLC.

Preparation of the complex $Cu(OAc)_2$-[10]



[**10**] $Cu(OAc)_2$-[**10**]

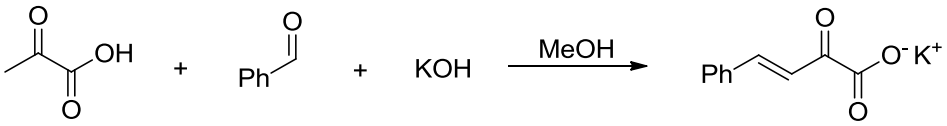
In a 2 mL dried vial 2.0 mg (0.011 mmol) of $Cu(OAc)_2$ and 7.1 mg (0.012 mmol) of [**10**] were weighted. Then 1 mL of absolute EtOH was added, leading to a gradually

dissolution of the ligand and to the observation of a green coloration, which turned to brownish after 24 hours. The absence of the free ligand was observed by TLC and the product formation was confirmed by electron spray analysis with positive ions ($MM_{product\ (calculated)}$ = 774 g/mol).

Mass (TOF ES+) = m/z 797 $(M + Na)^+$

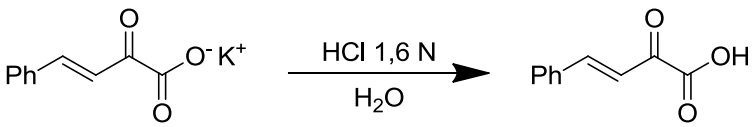
Mass (TOF ES+) = m/z 715 $(M - OAc)^+$

Synthesis of potassium benzylidenepyruvate[31]



In a 100 mL round-bottom flask were added 2.835 g (0.03219 mol) of pyruvic acid, 3.4235 g (0.03226 mol) of benzaldehyde and 2 mL of MeOH. To the resulting solution cooled in an ice-water bath was added a KOH solution in MeOH (2.76 g in 8.2 mL) as such a rate as to maintain the temperature at 15-20 °C. During the addition of the first two-thirds of the alkali a white precipitate was formed, then, after removal of the ice-bath, the last third of alkali solution was added rapidly observing a yellow precipitate and a reached temperature of 40 °C. After stirring 1 hour at 30 °C and 2 hours at 5 °C the yellow solid was filtered on a Büchner funnel, washed two times with MeOH and once with diethyl ether to obtain 5.7407 g of product (yield = 83%).

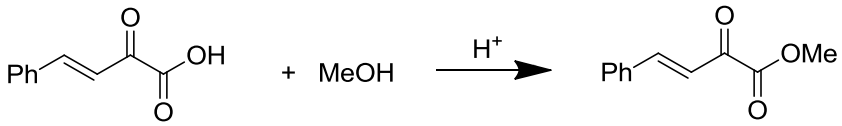
Synthesis of benzylidenepyruvic acid[31]



2.6211 g (0.012238 mol) of potassium benzylidene pyruvate was dissolved at 40 °C in the minimum quantity of water to obtain a saturated solution (around 30 mL) and rapidly added to 10 mL of a 1.6 N HCl solution. The solution became cloudy but without an

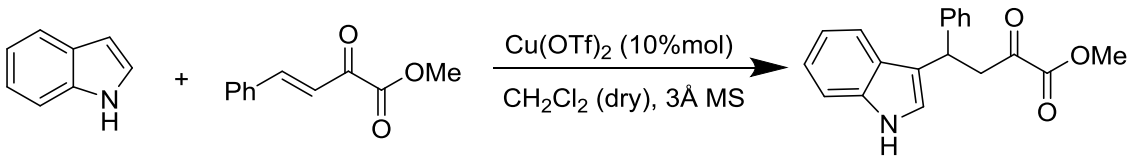
appreciable precipitation; instead the formation of an oil was observed. After rotavaporation of the water some toluene was added and rotavaporated few times to eliminate the water still present by azeotropic distillation. Thus the residue was dissolved in $CHCl_3$ and filtered over celite to remove the inorganic salt, KCl. The final evaporation of the organic solvent gave 2.1913 g of product (containing some solvent).

Synthesis of benzylidenepyruvic methyl ester



2.1913 g of crude benzylidenepyruvic acid were placed in a round-bottom flask with 60 mL of MeOH and 7 mL of a 2 N HCl solution in diethylether. The reaction mixture was heated until reflux in a Dean-Stark apparatus. After 2 hours at reflux the heating was removed and stirring continued overnight. The following rotavaporation yielded 1.807 g of crude product, which, after recrystallization from EtOH, gave 957 mg of the desired product in an overall 41% yield (from the potassium benzylidene pyruvate).
^{1}H NMR (300 MHz) δ 7.89 (d, J = 16.2 Hz, 1H), 7.67-7.62 (m, 2H), 7.48-7.41 (m, 3H), 7.38 (d, J = 16.1 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR in agreement with the one reported in literature.[29]

Friedel-Crafts reaction (Michael addition reaction) between methyl-(*E*)-2-oxo-4-phenyl-3-butenoate and indole catalyzed by Cu(OTf)$_2$.[28]



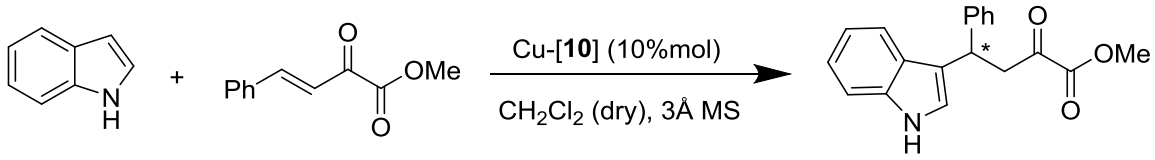
In a 2 mL dried round-bottom flask were weighted 36.1 mg (0.308 mmol) and 58.2 mg (0.306 mmol) of indole and methyl-(*E*)-2-oxo-4-phenyl-3-butenoate respectively. Then, under nitrogen flow, 1.5 mL of dry CH_2Cl_2 were added and the resulting solution cooled

to -70 °C. Subsequently 12.4 mg (0.0343 mmol) of $Cu(OTf)_2$ and around 30 mg of 3Å activated MS were added. After 20 minutes the reaction resulted complete by TLC. Thus the reaction mixture was filtered over celite and flash chromatographed. ^1H NMR in agreement with the one reported in literature.[28] HPLC with chiral column (AD-H column; 1.0 mL/min; Hexane:*i*-PrOH = 80:20; 25 °C, λ = 214 nm).

t_{R1} = 13.7 min

t_{R2} = 16.4 min

Friedel-Crafts reaction (Michael addition reaction) between methyl-(*E*)-2-oxo-4-phenyl-3-butenoate and indole catalyzed by the complex Cu-[10]

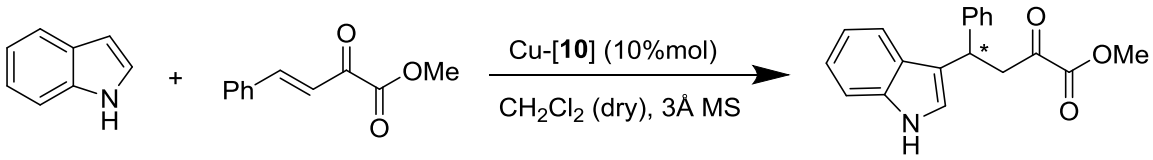


In a 2 mL dried round-bottom flask were weighted 8.0 mg (0.0221 mmol) and 13.2 mg (0.0223 mmol) of $Cu(OTf)_2$ and [**10**] respectively. Then 0.5 mL of dry CH_2Cl_2 were added and after some minutes around 25 mg of 3Å activated MS followed by further 0.2 mL of dry CH_2Cl_2 were added. After 2 hours of stirring 39.0 mg (0.206 mmol) of methyl-(*E*)-2-oxo-4-phenyl-3-butenoate were added, the reaction mixture cooled to -70 °C and stirred for 30 minutes before the addition of 24.3 mg (0.207 mmol) of indole. The reaction resulted complete after 5 minutes by TLC. Thus the quench of the active catalyst was performed adding some drops of water and the organic phase washed with a saturated solution of NH_4Cl. The aqueous phase was extracted with DCM; hence the reunited organic phases were dried over $MgSO_4$. After flash chromatography 45.0 mg of the product was obtained (yield = 72%) and the enantiomeric excess was determined by HPLC with chiral column (AD-H column; 1.0 mL/min; Hexane:*i*-PrOH = 80:20; 25 °C, λ = 214 nm), (ee = 52%).

t_R (minor enantiomer) = 13,7 min

t_R (major enantiomer) = 16,2 min

Friedel-Crafts reaction (Michael addition reaction) between methyl-(*E*)-2-oxo-4-phenyl-3-butenoate and indole catalyzed by the complex Cu-[10]

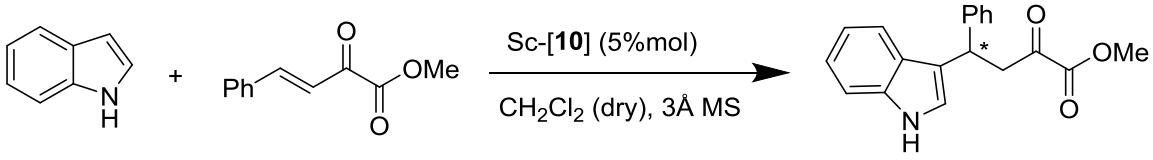


In a dried 5 mL round-bottom flask were weighted 4.2 mg (0.012 mmol) of $Cu(OTf)_2$ to which were added 2 mL of a suspension of [**10**] in dry CH_2Cl_2 prepared some days before (around 14.6 mg, 0.0246 mmol of ligand). Thus 60 mg of 3Å MS were added and the stirring continued for 2 hours resulting in an orange suspension. Then 39.2 mg (0.206 mmol) of methyl-(*E*)-2-oxo-4-phenyl-3-butenoate were added and stirred for 15 minutes at room temperature, after which the mixture was cooled to -75 °C. 15 minutes later 25.0 mg (0.213 mmol) of indole were added. The reaction mixture was stirred for one hour at – 70 °C for one hour was let warm until -30 °C. At the end of the 2 hours the reaction was complete by TLC and the formation of a solid was observed. The active catalyst was quenched with some drops of water and some DCM was added. The organic phase was washed with a saturated solution of NaCl, dried over $MgSO_4$ and flash chromatographed to obtain 52.0 mg of product (yield = 82%). The enantiomeric excess was determined by HPLC with chiral column (AD-H column; 1.0 mL/min; Hexane:*i*-PrOH = 80:20; 25 °C, λ = 214 nm), (ee = 63%).

t_R (minor enantiomer) = 13,6 min

t_R (major enantiomer) = 16,2 min

Friedel-Crafts reaction (Michael addition reaction) between methyl-(*E*)-2-oxo-4-phenyl-3-butenoate and indole catalyzed by the complex Sc-[10]

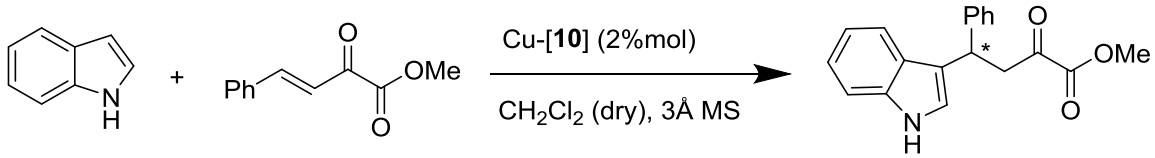


In a dried round-bottom flask 5.2 mg (0,011 mmol) of $Sc(OTf)_3$, 8.2 mg (0,014 mmol) of [**10**] and 31.6 mg of 3Å MS were stirred for 2 hours after adding 0.9 mL of dry CH_2Cl_2. Then 36.9 mg (0.194 mmol) of methyl-(*E*)-2-oxo-4-phenyl-3-butenoate were added and, after 20 minutes of stirring at room temperature, cooled to -70 °C. Thus 23.0 mg (0.196 mmol) of indole were added and the reaction mixture was let react for 3-4 hours maintaining the temperature between -80 and -65 °C. The usual workup with water was performed even if the reaction was not complete and after flash chromatography 35 mg of product were obtained (yield = 59 %). The enantiomeric excess was determined by HPLC with chiral column (AD-H column; 1.0 mL/min; Hexane:*i*-PrOH = 80:20; 25 °C, λ = 214 nm), (ee = 18 %).

t_R (minor enantiomer) = 13,8 min

t_R (major enantiomer) = 16,4 min

Friedel-Crafts reaction (Michael addition reaction) between methyl-(*E*)-2-oxo-4-phenyl-3-butenoate and indole catalyzed by the complex Cu-[10]

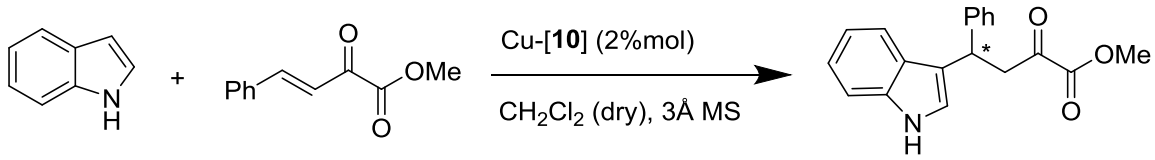


In a dried round-bottom flask were weighted 2.3 mg (0.0064 mmol) of $Cu(OTf)_2$ and 4.7 mg (0,0079 mmol) of [**10**]. Then around 25 mg of 3Å activated MS and 1 mL of dry CH_2Cl_2 were added. After 21 hours of stirring 57.0 mg (0.300 mmol) of methyl-(*E*)-2-oxo-4-phenyl-3-butenoate was added to the reaction mixture, cooled to -70 °C and after further 30 minutes 36.4 mg (0.311 mmol) of indole were added. Two hours later the active catalyst was quenched with some drops of water. The organic phase washed with brine, dried over $MgSO_4$ and flash chromatographed to obtain around 38 mg of product (yield = 41 %). The enantiomeric excess was determined by HPLC with chiral column (AD-H column; 1,0 mL/min; Hexane:*i*-PrOH = 80:20; 25 °C, λ = 214 nm), (ee = 46%).

t_R (minor enantiomer) = 13,6 min

t_R (major enantiomer) = 16,2 min

Friedel-Crafts reaction (Michael addition reaction) between methyl-(*E*)-2-oxo-4-phenyl-3-butenoate and indole catalyzed by the complex Cu-[10]

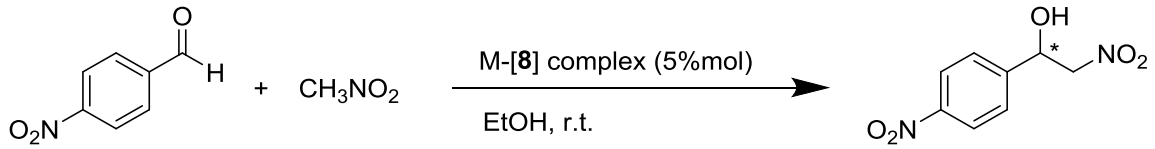


In a dried round-bottom flask were weighted 4.6 mg (0,013 mmol) of $Cu(OTf)_2$ and 8.7 mg (0,015 mmol) of [**10**]. Then around 35 mg of 3Å activated MS and 1 mL of dry CH_2Cl_2 were added. After 2 hours of stirring 38.0 mg (0,200 mmol) of methyl-(*E*)-2-oxo-4-phenyl-3-butenoate were added to the reaction mixture, cooled to -70 °C and after 30 minutes 26,5 mg (0,226 mmol) of indole were added. 70 minutes later the active catalyst was quenched with some drops of water. The organic phase washed with a saturated solution of NaCl, dried over $MgSO_4$ and flash chromatographed to obtain around 49 mg of product (yield = 80%). The enantiomeric excess was determined by HPLC with chiral column (AD-H column; 1.0 mL/min; Hexane:*i*-PrOH = 80:20; 25 °C, λ = 214 nm), (ee = 28%).

t_R (minor enantiomer) = 13,9 min

t_R (major enantiomer) = 16,5 min

Henry reaction between *p*-nitrobenzaldehyde and nitromethane catalyzed by the various complexes Mn-, Ni-, Cu- and Co-[8].[32]



0.010 mmol of metal salt and 0.011 mmol of [**8**] were placed in a flame-dried vial. 1 mL of absolute EtOH was added and, almost immediately, it was observed the formation of an intense colored solution. After 90 minutes of stirring 31.8 mg (0.210 mmol) of *p*-nitrobenzaldehyde were added, followed, one hour later, by 125 µL (11 eq.) of nitromethane. The stirring reaction mixture was let react at room temperature for 48 hours, thus rotavaporated and flash chromatographed (EtOAc:Hexane = 1:4.5) to obtain

the product in a quantitative yield. ^{1}H NMR in agreement with the one reported in literature.[32] The enantiomeric excess was determined by HPLC with chiral column (OD-H column; Hexane:*i*-PrOH = 85:15; 0.8 mL/min; 25 °C; λ = 254 nm).

t_R (minor enantiomer) = 19.9 min

t_R (major enantiomer) = 24.7 min

Catalyst and enantiomeric excess:

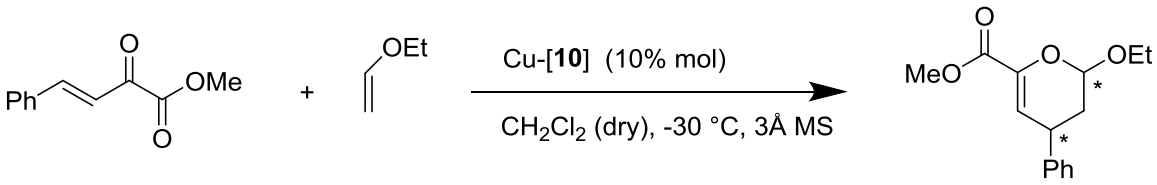
Ni-[**8**] complex (metal source: $Ni(OAc)_2 \cdot 4H_2O$), ee = 20 %

Cu-[**8**] complex (metal source: $Cu(OAc)_2$), ee = 10 %

Mn-[**8**] complex (metal source: $Mn(OAc)_2 \cdot 4H_2O$), ee = 5 %

Co-[**8**] complex (metal source: $Co(OAc)_2 \cdot 4H_2O$), ee = 0 %

Diels-Alder reaction between benzylidenepyruvic methyl ester and ethyl vinyl ether catalyzed by the complex Cu-[10].[29]



In a flame-dried round-bottom flask 9.1 mg (0.025 mmol) of $Cu(OTf)_2$ and 15.8 mg (0.027 mmol) of [**10**] were weighted, thus, after adding 1 mL of dry CH_2Cl_2, the mixture was stirred for around 60 hours, the resulting suspension became a green solution after that 35 mg of 3Å MS were added. Thus the catalyst solution was cooled to -30 °C and, one hour later 43.7 mg (0.230 mmol) of methyl-(E)-2-oxo-4-phenyl-3-butenoate were added to the reaction mixture, followed by around 100 µL (around 4 eq) of ethyl vinyl ether after 30 minutes. After stirring for around 20 hours at -30 °C the reaction mixture was directly chromatographed using DCM:Hexane = 1:2 as eluent. The two diastereoisomers eluted were analyzed by ^{1}H NMR which showed a dr from 79:21 to 60:40. The enantiomeric excess of the two different diastereoisomers was determined by HPLC with chiral column (OJ-H column; Hexane:*i*-PrOH = 98:2; 0.5 mL/min; 25 °C; λ = 230 nm) which showed an ee from 30 to 70 % for the first pair of enantiomers [t_R (minor enantiomer) = 27 min; t_R (major enantiomer) = 76 min] and an ee from 0 to 40 %

for the second one [t_R (major enantiomer) = 29 min; t_R (minor enantiomer) = 120 min]. Using a different chiral colum (IC column; Hexane:*i*-PrOH = 98:2; 1 mL/min; 25 °C; λ = 230 nm) the two enantiomers of the first diastereoisomer had the t_R = 11.6 and 16.2 min while the second pair relative to the second diastereoisomer had the t_R = 24.4 and 26.0 min. The first pair of enantiomers was determined as the endo (trans) isomer by comparison with the literature.[29,33]

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