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Novel tridentate ligands and their molybdenum complexes in oxidation reactions

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Kiss Eleonóra

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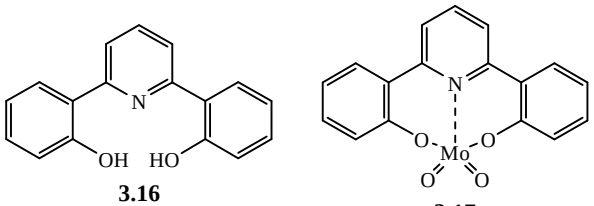
Abstract

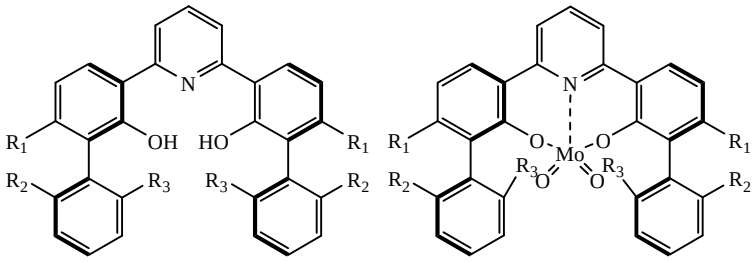
With the desire to work on the development of new organometallic catalysts suitable for asymmetric epoxidation and sulfoxidation, we have focused our research efforts on molybdenum catalysts bearing novel tridentate chiral ligands. The good catalytic activity displayed by some pyridine-diol molybdenum complexes prompted our interest in the more rigid **3.16** diaryloxy-pyridine as ligand skeleton.



3.16 **3.17**

Scheme 1

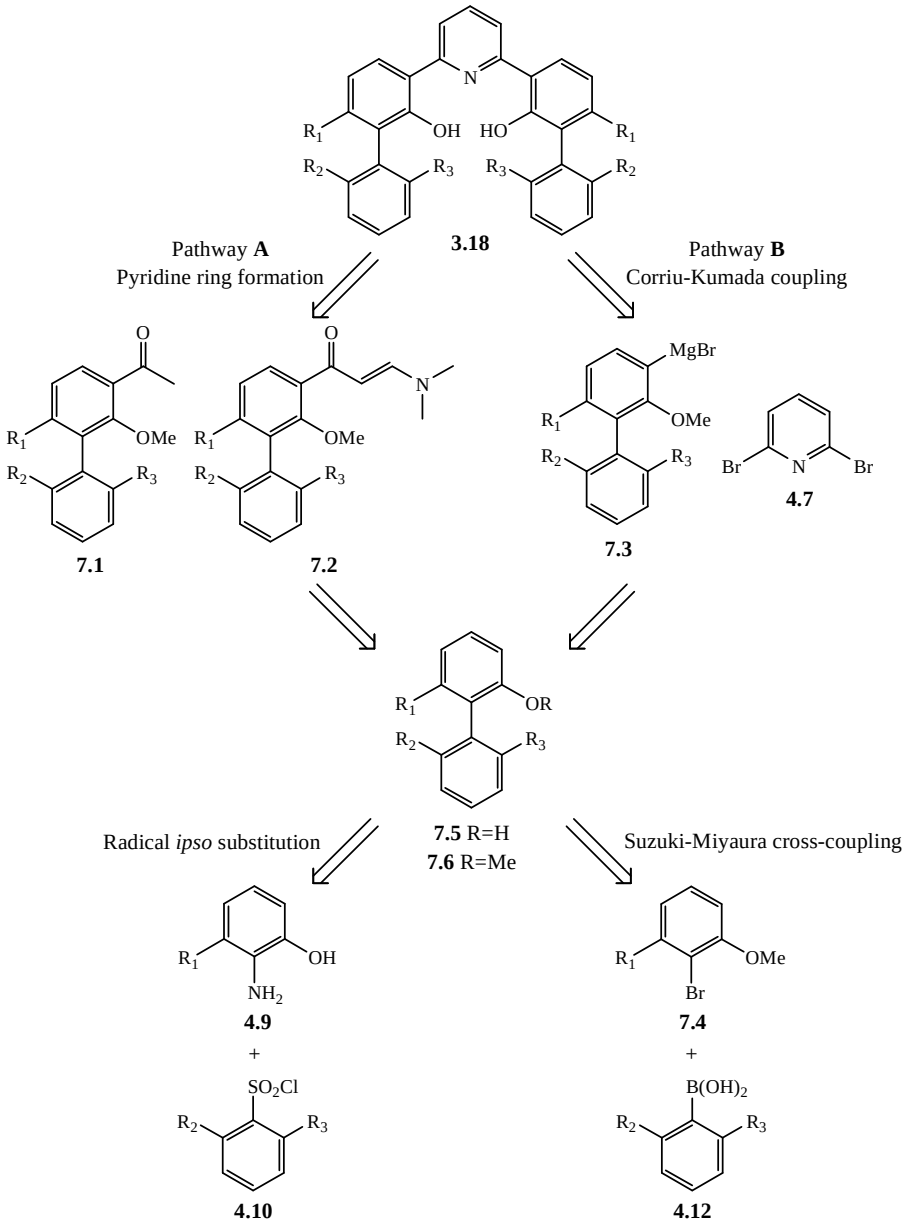
After ensuring that good catalytic activity was reached for the corresponding molybdenum complex **3.17**, the main objective of the present thesis was to extend our study to diaryloxy-pyridine ligands **3.18**, bearing axial chirality on the phenol fragments.



3.18 **1**

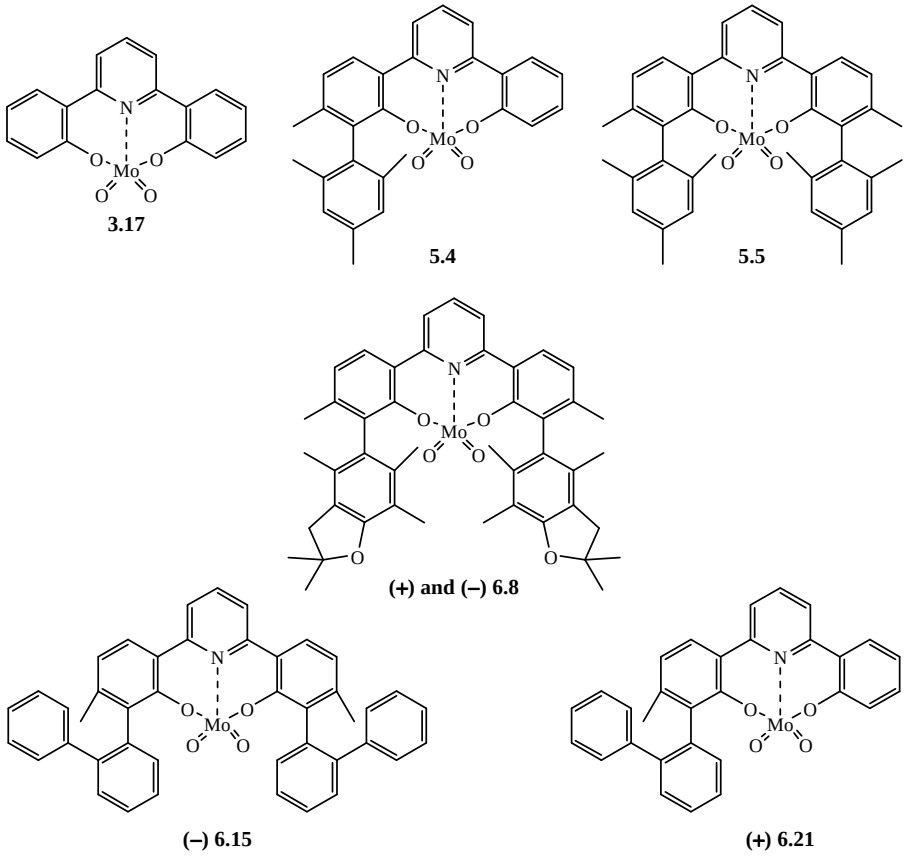
Scheme 2

Different general synthetic strategies have been developed for the formation of such ligand skeleton (*Scheme 3*).



Scheme 3

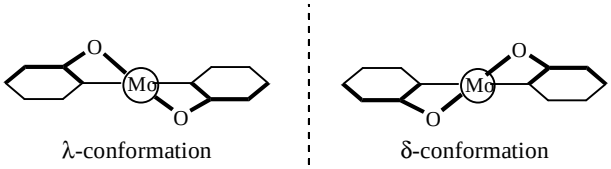
After a detailed study of these pathways during the synthesis of the achiral model ligands, the chiral diaryloxy-pyridines have been prepared using suitable enantiopure biphenyl fragments.



Scheme 4

The corresponding *cis*-MoO_2 complexes have been formed and, apart from complex (-)-**6.15**, they have been isolated and fully characterized. An important structural feature of these complexes has been revealed from single crystal X-ray diffraction analyses. The phenolic oxygens are positioned diagonal to each other, one above and the other one below the plane of the pyridine ring (*Scheme 5*). The significant twist imparted to the molecule suggests the existence of

two enantiomeric forms in the case of the achiral ligands and two possible diastereomeric forms in the case of the chiral, enantiopure ligands. However, the stability of these conformations has not been measured yet. Additionally, complexation of the chiral, enantiopure ligands was either diastereoselective or the diastereomeric forms could not be differentiated by NMR spectroscopy, which would be somewhat surprising.



Scheme 5

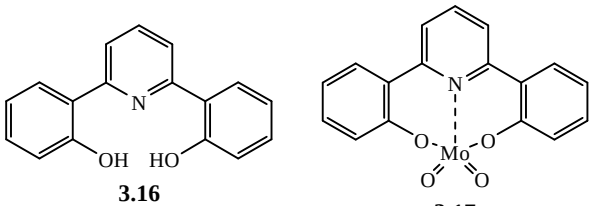
All of the prepared complexes proved to be active epoxidation and sulfoxidation catalysts. Unfortunately, the optically active complexes did not induce asymmetry under our reaction conditions.

In general, electron rich sulfides, alkenes and allylic alcohols were oxidized faster compared to styrene derivatives or terminal alkenes. Geraniol was regioselectively epoxidized at the double bond proximal to the hydroxyl function. Additionally, epoxidation of 1,2-disubstituted alkenes was shown to be completely stereospecific.

An interesting structure-reactivity relationship has been observed while comparing the reactivity of complexes **3.17**, **5.4** and **5.5** in the epoxidation of *trans-β*-methyl-styrene and 1-octene. Increasing the size of the catalyst improved the reactivity of the molybdenum complex in these reactions. On the other hand, in the case of more electron rich substrates, the three catalysts displayed high, though essentially similar reactivities.

Résumé

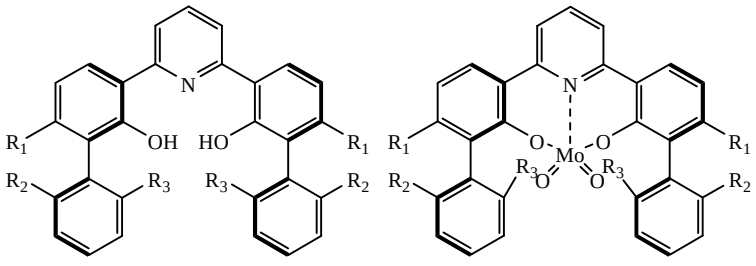
Afin de développer des catalyseurs organométalliques appropriés pour l'époxydation d'alcènes et l'oxydation de sulfures, nous avons focalisé notre recherche sur des catalyseurs au molybdène décoré de nouveaux ligands chiraux tridentates. Des études récentes concernant des complexes du molybdène portant un ligand diol-pyridine ont démontré une très bonne activité mais une absence d'énantiosélectivité. Dès lors, notre attention s'est tournée vers des ligands plus rigides **3.16**, du type diaryloxypiridine (*Schéma 1*).



3.16 **3.17**

Schéma 1

Après avoir démontré l'efficacité de l'activité catalytique du complexe de molybdène **3.17**, utilisé comme modèle, nous avons concentré nos efforts sur l'étude de ligands diaryloxy-pyridine **3.18**, possédant un axe de chiralité sur la partie phénolique.



3.18 **1**

Schéma 2

Différentes stratégies de synthèse pour accéder à ces ligands, ont été envisagées et étudiées (*Schéma 3*).

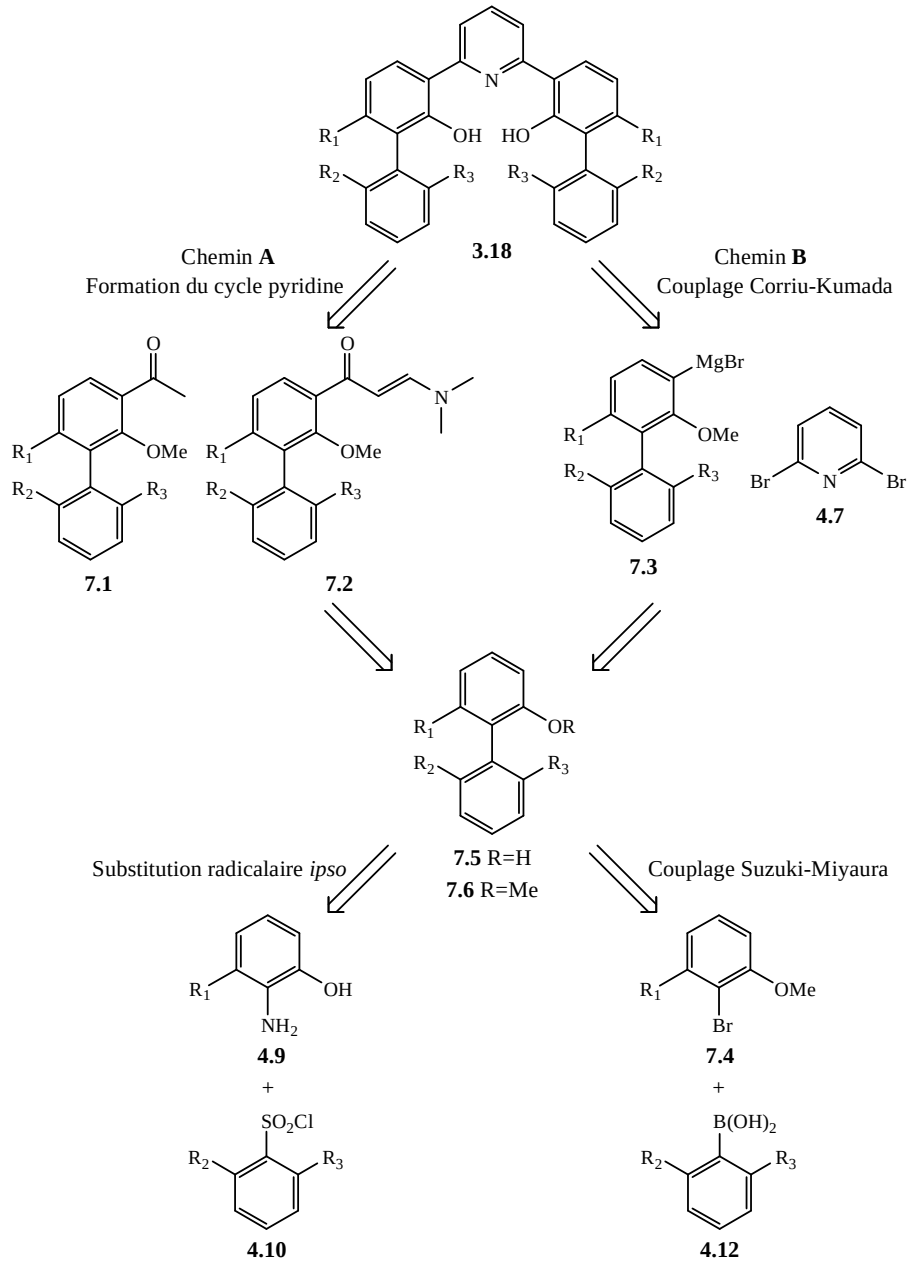


Schéma 3

Après une étude en profondeur de ces divers chemins synthétiques sur des ligands achiraux, les molécules chirales diaryloxy-pyridines ont été préparées au départ des fragments diphényles énantiopurs appropriées.

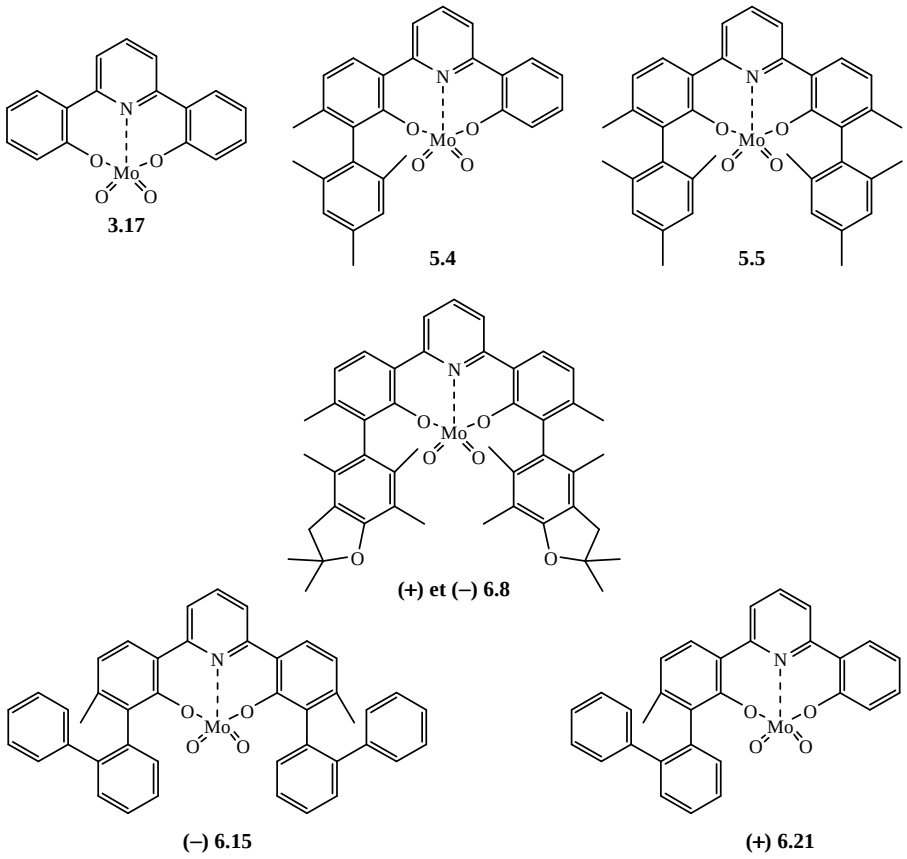


Schéma 4

Les complexes *cis*-MoO_2 ont été préparés avec succès (*Schéma 4*). A l'exception du composé (-)-**6.15**, tous ces complexes ont été isolés et complètement caractérisés. Les analyses par diffraction des rayons X ont mis en évidence une caractéristique structurale importante de ces complexes. En effet, les oxygènes phénoliques sont positionnés diagonalement l'un part rapport à l'autre; l'un au-dessus et

l'autre en dessous du plan formé par le cycle pyridinique (*Schéma 5*). Il est clair que l'existence de ces deux conformères donne naissance à des complexes énantiomères lorsque les ligands sont achiraux, et à des diastéréoisomères si les ligands sont énantiopurs. Toutefois, la stabilité de ces conformations n'a pas été étudiée en détail. De plus, après la complexation des diaryloxy-pyridines chirales énantiopurs, différentes expériences de résonance magnétique nucléaire n'ont pas mis en évidence l'existence de deux diastéréoisomères. Dès lors, on peut supposer que la formation du complexe est diastéréosélective ou que les deux formes en équilibre ne peuvent pas être différenciées par la RMN, ce qui serait relativement étonnant.

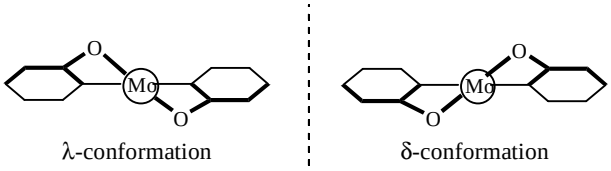


Schéma 5

Tous les complexes préparés ont démontré une excellente activité catalytique lors de la formation d'époxydes et de sulfoxydes. Malheureusement, dans les conditions réactionnelles employées, les complexes optiquement actifs n'ont pas conduit à une induction asymétrique.

En général, nos catalyseurs ont époxydé plus rapidement les alcènes électroniquement riches et les alcools allyliques, que les dérivés du styrène et les oléfines terminales. Dans le cas de l'époxydation du géraniol, la double liaison la plus proche de la fonction hydroxyle a été sélectivement oxydée. De plus, l'époxydation des oléfines 1,2-disubstituées est complètement stéréospécifique. Il est

à noter que l'oxydation des sulfures est plus rapide que la réaction d'époxydation.

Ce travail a également permis de montrer une très intéressante relation structure-réactivité entre les complexes **3.17, 5.4** et **5.5** lors de l'époxydation du *trans-β*-méthyl-styrène et du 1-octène. Lors de ces réactions, un accroissement de la taille du ligand a entrainé une augmentation de l'activité du complexe de molybdène. Cependant, ces trois catalyseurs ont démontré une réactivité similaire durant l'oxydation des substrats électroniquement plus riches.

Symbols and abbreviations

A

Å	Ångstrom (10^{-10} meter)
$[\alpha]^{D}_{21}$	optical rotation using the sodium D line (589 nm) at 21°C
Ac	Acetyl
acac	acetyl acetonate
Alk	Alkyl group
APCI	Atmospheric Pressure Chemical Ionization
aq.	aqueous
Ar	Argon or Aryl group

B

BINOL	1,1'-bi-2-naphthol
Bn	Benzyl group
bs	broad signal or broad singlet
Bu	Butyl group
Bz	Benzoyl group

C

°C	degrees Celsius
c-	*cyclo*-
cat.	catalytic quantity or catalyst

cc.	concentrated
CHP	cumyl hydroperoxide
CI	Chemical Ionization
Cys.	Cystein
D	
δ	chemical shift
d	doublet
dba	dibenzylidene acetone
DBAD	di-*tert*-butyl azodicarboxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DET	diethyl tartrate
DMAE	2-dimethylaminoethanol
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppe	1,2-*bis*(diphenylphosphino)ethane
E	
E	electrophile
EDTA	ethylenediaminetetraacetic acid

ee	enantiomeric excess
EI	Electronic Impact
eq.	equivalent
ESI	Electron Spray Ionization
Et	ethyl
G	
g	gram
GC	Gas Chromatography
H	
h	hour
hfc	3-(heptafluoropropylhydroxymethylene)-*d*-camphorate
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
Hz	Hertz
I	
i-	*iso*-
Int.	integration
IR	Infra Red
J	
J	coupling constant
K	

KHMDS	potassium hexamethyldisilazide
L	
LDA	lithium diisopropylamide
LiTMP	lithium tetramethylpiperidine
M	
µl	microlitre
M	molar (mol/dm^3)
m	multiplet or medium
Me	methyl group
mg	milligram
MHz	megahertz
min.	minutes
ml	millilitre
mmol	millimol
MOM	methoxymethyl
MPLC	Medium Pressure Liquid Chromatography
MS	Mass Spectrometry or molecular sieves
m/z	mass per charge
N	
n-	*normal*-
N	normality

N°	number
NBS	*N*-bromosuccinimide
NMR	Nuclear Magnetic Resonance
O	
o-	*ortho*-
O/N/O	tridentate ligand bearing oxygen/nitrogen/oxygen donor atoms
Oxone	potassium peroxomonosulfate ($2\ KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$)
P	
PE	petroleum ether
Ph	phenyl group
pH	potentiometric hydrogen ion concentration
ppm	part per million
Pr	propyl group
Q	
q	quadruplet
R	
R_f	retention factor
RT	room temperature
S	
s-	secondary-

s	singlet (NMR) or strong (IR)
salen	*N,N'*-ethylenebis(salicylimine)
solv.	solvent
T	
t	triplet
t-	*tertiary*-
TBHP	*t*-butylhydroperoxide
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	tetramethylethylenediamine
TMS	tetramethylsilane or trimethylsilyl group
TPPP	tetraphenylphosphonium monoperoxysulfate
TRISPHAT	tris[tetrachlorobenzenediolato]phosphate(V)
U	
UHP	urea-hydrogen peroxide complex
W	
w	weak
X	
X	halide group

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Preface

Enantioselective synthesis of chiral organic molecules represents a fascinating area of academic research, which has stimulated an increasing interest from chemical industries. Most importantly, it became essential for pharmaceutical industry. It has been recognized that, while one enantiomer of a biologically active molecule has the desired effect, the other enantiomer can be less-effective, non-effective or display negative side-effects. Therefore, enantiomers of new chiral drugs should be separately tested before commercializing them, even in the racemic form.

There are three major possibilities to obtain organic molecules in enantiopure form: resolution of racemic mixtures, stereospecific transformation of naturally occurring enantiopure compounds and asymmetric synthesis. A serious drawback of the classical resolution methods is that they are limited to *50%* chemical yield. However, an increasing number of dynamic kinetic resolution procedures are presented to overcome this limitation. The natural "chiral pool" being limited as well, the development of asymmetric synthetic methods became necessary.

The main asymmetric inducing strategies are based on the use of chiral auxiliaries, chiral reagents or chiral catalysts. In theory, the latter one, using the chiral inducer in sub-stoichiometric amount, would be the ideal choice for industrial scale synthesis. Biological systems, small organic molecules and organometallic complexes of chiral ligands are continuously being tested for this purpose.

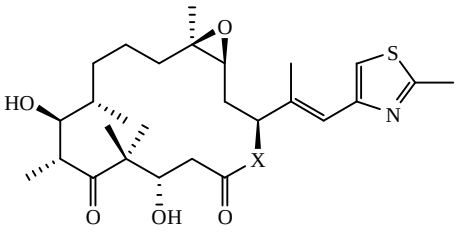
Our interest in this area lies in the development of new organometallic catalysts suitable for asymmetric epoxidation and sulfoxidation. Our research has been focused on molybdenum and vanadium catalysts bearing novel tridentate chiral ligands.

Before describing our strategy and the obtained results, we will shortly explain why enantiopure epoxides and sulfoxides are such valuable compounds and we will highlight the most important catalytic methods for their preparation.

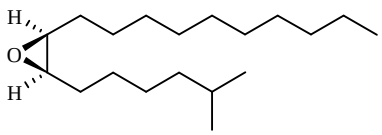
I. Catalytic asymmetric epoxidation of alkenes

I. 1. Introduction

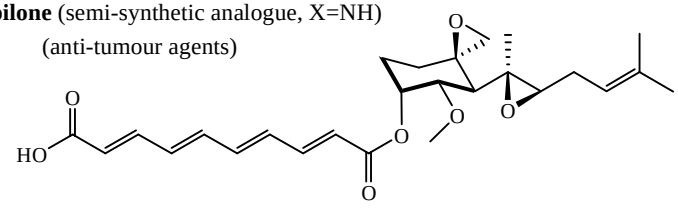
A large number of optically active epoxides have been isolated from living organisms and studied for their important biological properties. Among them, we can find insect pheromones, such as disparlure, and more importantly, several potent anti-tumour and anti-biotic agents. Representative examples are shown in the scheme below.



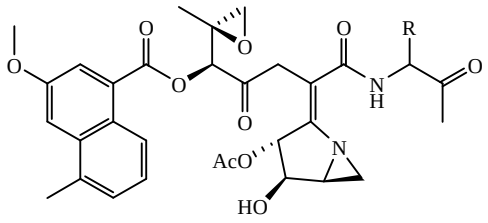
1.1 Epothilone B (X=O)
1.2 Ixabepilone (semi-synthetic analogue, X=NH)
(anti-tumour agents)



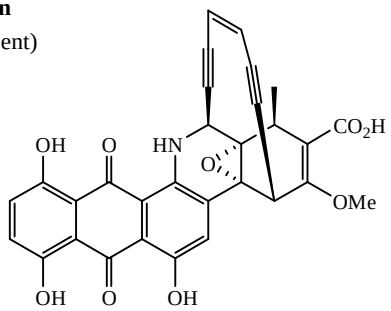
1.3 Disparlure
(insect pheromone)



1.4 Fumagillin
(anti-parasitic agent)



1.5 Azinomycin A (R=H)
1.6 Azinomycin B (R = CH=CHOH)
(antibiotic, anti-tumour agents)



1.7 Dynemicin A
(anti-tumour agent)

Scheme 6

Only few of these natural compounds bear already the required pharmacological profile to be approved for medication, but they serve as model for the synthesis of future drugs.[1] Numerous epothilone, azinomycin and dynemicin analogues are currently being tested for their anti-tumour activities. Ixabepilone **1.2**, a semi-synthetic analogue of the natural epothilone B, is already approved and applied for the clinical treatment of metastatic and advanced breast cancers. A further example of biologically active epoxides is fumagillin **1.4**, a fungal metabolite, which is used as an anti-parasitic drug in the treatment of microsporidiosis, an intestinal infection frequent in and fatal for immuno-compromised patients.

Contrary to the above mentioned properties of certain oxirane-containing molecules, optically active epoxides are most frequently used as key intermediates in fine organic synthesis.[2] Due to the strain of the three-membered ring, the oxirane heterocycle exhibits a synthetically useful balance between stability and reactivity. The versatility of epoxides as intermediate lies in the fact that they can be ring opened with a broad range of nucleophiles with high or complete stereoselectivity and regioselectivity. Thus, formation and ring opening of an enantiopure epoxide offers the possibility to introduce two adjacent chiral centres with very high selectivity and atom economy.

[1] a. Mulzer J.; Altmann K-H.; Höfle G.; Müller R.; Prantz K. *C. R. Chimie* **2008**, *11*, 1336; b. Nicolau K. C.; Chen J. S.; Dalby S. M. *Bioorg. Med. Chem.* **2009**, *17*, 2290; c. Hashimoto M.; Matsumoto M.; Yamada K.; Terashima S. *Tetrahedron* **2003**, *59*, 3089; d. Myers A. G.; Kort M. E.; Cohen S. B.; Tom N. J. *Biochemistry* **1997**, *36*, 3903

[2] a. Yudin A. K. *Aziridines and Epoxides in Organic Synthesis* **2006**, Wiley-VCH, Weinheim; b. Padwa A.; Murphree S. S. *Arkivoc* **2006**, *3*, 6

Due to the significant utility of enantiopure epoxides in the synthesis of sophisticated biologically active compounds, several chemical and biological methods have been developed for their preparation. Without any doubt, one of the most convergent, elegant and atom economic method for the preparation of enantiomerically enriched epoxides is the catalytic asymmetric epoxidation of alkenes.[3] The most important methods in this field will be detailed in the following paragraphs.

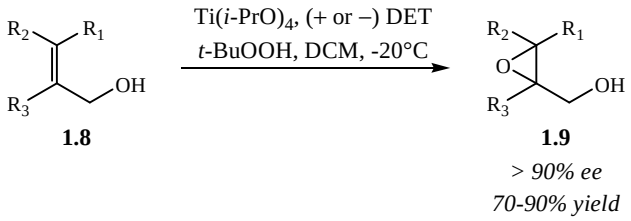
Being limited to allylic alcohols, but representing a fundamental discovery in asymmetric catalysis, the Sharpless-Katsuki epoxidation system will be presented first. Then, we will turn our attention to the most important biological, organometallic and organic catalytic systems being developed for the epoxidation of simple olefins. Afterwards, we will describe the most significant asymmetric catalytic methods for the epoxidation of electron deficient olefins based on the Weitz-Scheffer reaction. And finally, a few additional promising oxidation systems will be shown. Focusing on the direct oxidation of alkenes, kinetic resolution of racemic epoxides and synthetic methods based on halohydrins or aldehyde and ketone precursors, such as ylide-mediated or Darzens reaction, will be omitted.

I. 2. Sharpless-Katsuki epoxidation

In 1980, Sharpless and Katsuki discovered, that the reaction of allylic alcohols with *tert*-butyl hydroperoxide (TBHP) in the presence

[3] Recent reviews: a. Bonini C.; Righi G. *Tetrahedron* **2002**, *58*, 4981; b. Xia Q-H.; Ge H-Q.; Ye C-P.; Liu Z-M.; Su K-X. *Chem. Rev.* **2005**, *105*, 1603

of Ti(*i*-PrO)$_4$ and enantiopure diethyl tartrate (DET) gave epoxy alcohols with high enantiomeric purities.[4]



1.8 **1.9**

> 90% ee

70-90% yield

Scheme 7

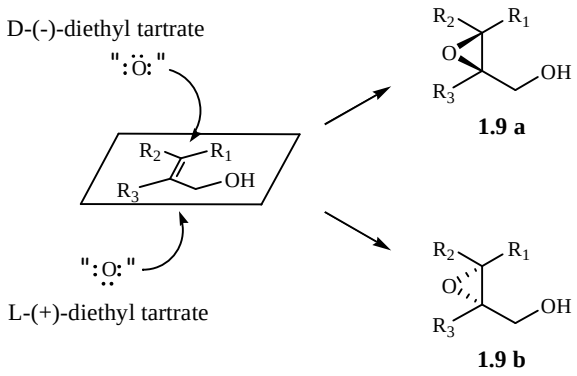
In the original condition, the use of stoichiometric amounts of titanium tartrate is necessary except for very reactive substrates. A few years later, however, they found that addition of activated molecular sieves enables most of the reactions to be carried out with only 5-10% of titanium tartrate catalyst.[5] It turned out that the presence of water lowers the enantioselectivity and the rate of the reaction by interacting both reversibly and irreversibly with the catalyst.

The catalytic condition is not only more economic but it has several other advantages.[6] The milder reaction conditions and easier product isolation result in higher yields in the case of sensitive epoxides. However, it has to be mentioned, that the enantioselectivities are slightly depressed (by 1-5%), compared with the stoichiometric conditions. The author empathizes, that one of the major advantages of the catalytic method, is, that *in situ* derivatization of the forming epoxide became also possible, saving the highly water

[4] Katsuki T.; Sharpless B. *J. Am. Chem. Soc.* **1980**, *102*, 5976
[5] Hanson R. M.; Sharpless K. B. *J. Org. Chem.* **1986**, *51*, 1922
[6] Gao Y.; Hanson R. M.; Klunder J. M.; Ko S. Y. Masamune H.; Sharpless K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765

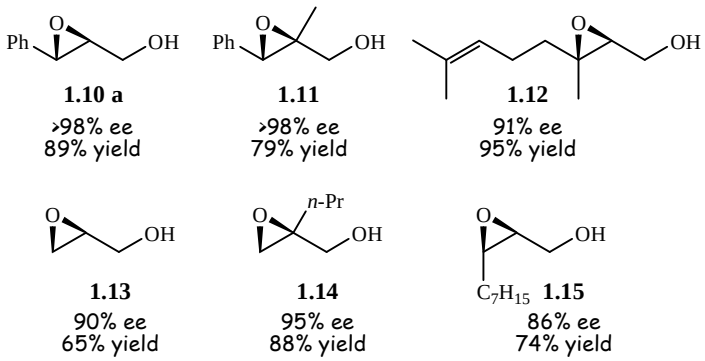
soluble epoxides in their more stable, easily isolable and still synthetically very useful form.

Importantly, it has been recognized that the stereochemistry of the epoxide products depends on the diethyl tartrate used in the reaction. Drawing the allylic alcohol in a plane with its hydroxyl function on the right side as shown in *Scheme 8*, the unnatural D-(-)-diethyl tartrate directs the attact of the oxidizing agent from the top whilst the natural L-(+)-diethyl tartrate delivers the oxygen from below the plane. Therefore, the stereochemistry of the epoxidation can be easily predicted.



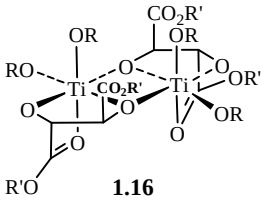
Scheme 8

(*E*)-allylic alcohols proved to be the best substrates, leading to high enantioselectivities with this method. In the case of (*Z*)-allylic alcohols, the enantioselectivity is significantly influenced by the nature and the size of the R_1 substituent. A few, representative examples of the best results, obtained under the improved catalytic conditions, can be seen below.



Scheme 9

A number of studies have been carried out by Shapless and co-workers to elucidate the mechanism of the reaction.[7] They found that the active catalyst is probably a dimer in which two titanium atoms are connected by two tartrate molecules forming a ten-membered ring (*Scheme 10*). The tartrate ester groups extend outward from this ring, directing the approach of the allylic alcohol and hydroperoxide to the metal center.

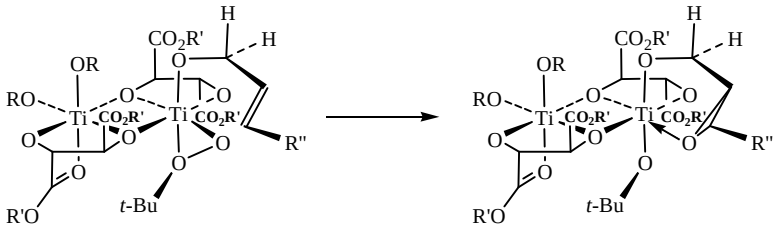


Scheme 10

It is proposed that the allylic alkoxide is bound *trans* to the coordinated ester and the *tert*-butyl peroxide *cis* to the same carbonyl. Subsequent carbonyl dissociation occurs to achieve the bidentate coordination of the alkyl peroxide (*Scheme 11*). Finally, S_N2 type

[7] Burns C. J.; Martin C. A.; Sharpless K. B. *J. Org. Chem.* **1989**, *54*, 2826

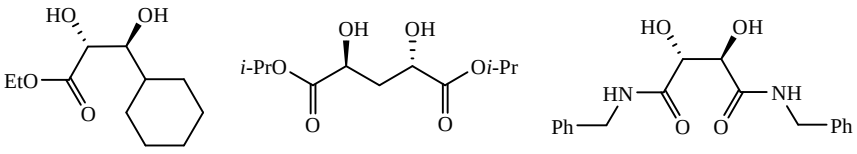
attack of the double bond onto the peroxide's oxygen results in the formation of the epoxide ring.



1.17 **1.18**

Scheme 11

Several modifications of the original asymmetric epoxidation system have been studied. A rather extensive ligand survey has been carried out by Sharpless and coworkers on more than 50 ligands.[8] Three representative examples are depicted in *Scheme 12*.



1.19 **1.20** **1.21**

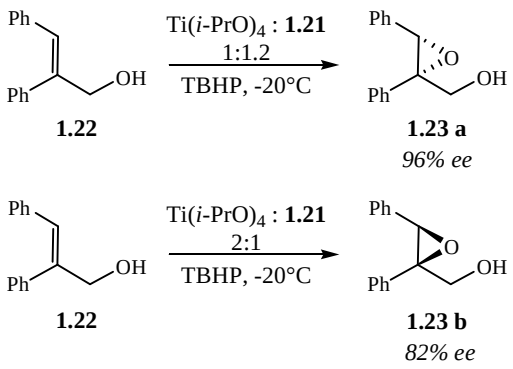
Scheme 12

From their study, they concluded that three out of the four functions of the tartrate ester are necessary to obtain an enantioselective catalyst for the epoxidation reaction. For example ligand **1.19**, where one of the ester functions of the tartrate is replaced by a cyclohexyl group, proved to be a useful ligand in asymmetric epoxidation. Additionally, ligand **1.20**, where there is an extra methylene unit compared to the tartrate, behaves similarly to the

[8] a. Lu L. D-L.; Johnson R. A.; Finn M. G.; Sharpless K. B. *J. Org. Chem.* **1984**, *49(4)*, 728; b. Burns C. J.; Martin C. A.; Sharpless K. B. *J. Org. Chem.* **1989**, *54*, 2826

original ligand regarding the rate and enantioselectivity of the epoxidation.

Study of tartrate amide **1.21**, as ligand, led to an interesting observation (*Scheme 13*). Using different ratios of Ti(*i*-PrO)$_4$ and ligand **1.21**, the enantiofacial selection could be inverted. When the standard 1 to 1.2 ratio is used, the enantioselectivity is in the same sense than in case of tartrate esters. However, when a 2 to 1 ratio is employed, the opposite enantiomer forms preferentially. The structure of the active catalytic species is obviously not the same in these two systems. Moreover, the efficiency of ligand **1.21** proved to be strongly substrate dependent.



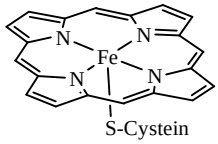
Scheme 13

Despite the fact that the Sharpless system is limited to allylic alcohols and sensitive to pre-existing chirality in the substrate, it is still frequently used in asymmetric synthesis. Its discovery was not only a breakthrough in enantioselective epoxidation of alkenes, but in asymmetric synthesis in general.

I. 3. Biocatalytic approaches and porphyrin systems

Purified enzymes, whole-cell organisms and genetically engineered strains have also been tested for the direct epoxidation of C-C double bonds.[9] The success of these biological systems stays far behind the current chemical methods. However, since the study of heme-dependent oxygenating enzymes played an important role in the early development of asymmetric organometallic catalysis, we will briefly describe some of these biological catalysts.

P-450 enzymes are present in many living organisms: insects, plants, yeasts, fungi and mammals. Their role in the living cells includes the transformation of toxic hydrophobic xenobiotics to water soluble metabolites that can be easily eliminated from the cell. They are monooxygenases, which means that they are able to incorporate one of the two oxygen atoms of the activated molecular oxygen into an organic molecule. Their catalytically active site is a ferroporphyrin bound to a cystein thiolate group of the chiral protein molecule (*Scheme 14*). The chiral cavity discriminates the potential substrates which are oxidized by the previously formed Fe(V)=O porphyrin species.



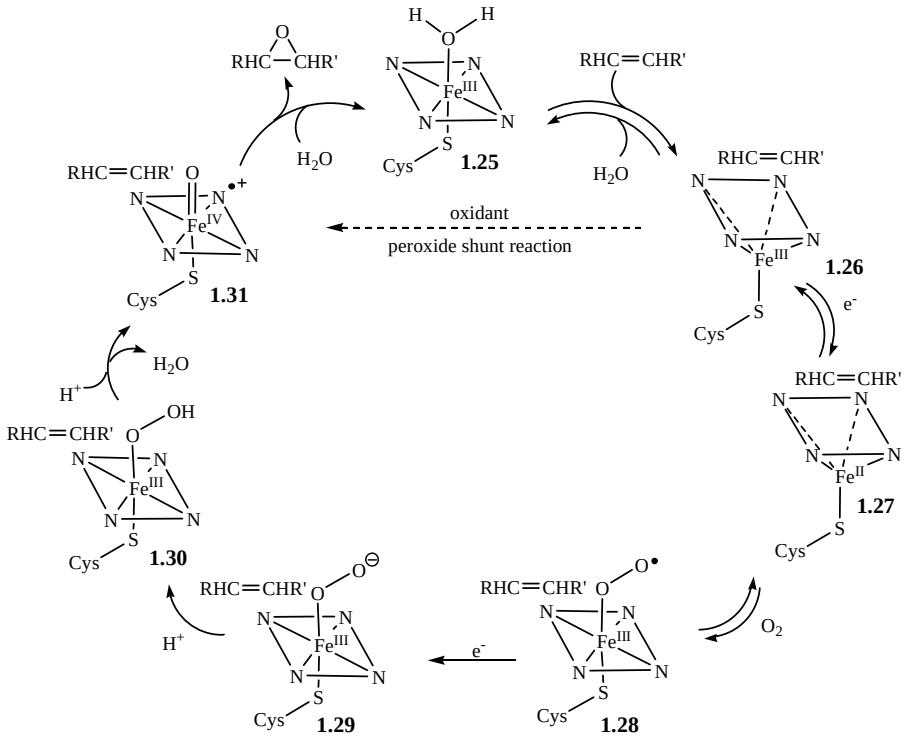
Scheme 14

Around thirty isozymes of cytochrome P-450 have been isolated and some of them were tested in the asymmetric epoxydation

[9] Archelas A.; Furstoss R. *Annu. Rev. Microbiol.* **1997**, *51*, 491

of alkenes. Unfortunately, and in analogy to other, non-heme dependent monooxygenase enzymes, their use is limited to certain alkenes.[10] The enantiomeric excess of a particular epoxide is highly dependent on the organism employed. A further drawback on large scale synthesis is that low concentrations (10-100 mM) are needed since the generated reactive epoxide can inhibit the producing organism.

The proposed catalytic cycle is shown in *Scheme 15*.[11]



Scheme 15

[10] de Bont J. A. M. *Tetrahedron: Asymmetry* **1993**, *4(6)*, 1331

[11] a. Sono M.; Roach M. P.; Coulter E. D.; Dawson J. H. *Chem. Rev.* **1996**, *96*, 2841; b. Rose E.; Andrioletti B.; Zring S.; Quelquejeu-Ethève M. *Chem. Soc. Rev.* **2005**, *34*, 573

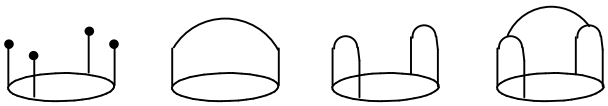
At the beginning of the catalytic cycle, the iron(III) porphyrin exists in its six-coordinated low spin state. The approach of a substrate molecule expels the coordinating water, affording a five-coordinated high spin iron(III) complex **1.26**. The uptake of an electron followed by the binding of an oxygen molecule results in a low spin iron(III) superoxide complex **1.28**. The formation of the peroxy species by the uptake of a second electron seems to be the rate determining step of the cycle. By the subsequent uptake of two protons and elimination of water a high-valent iron-oxo intermediate **1.31** is generated. It is formally an iron(V)-oxo species, but actually it is thought to be an oxoiron(IV) radical cation complex where one oxidizing equivalent is stored in the ligand. This species transfers its oxygen atom to the substrate and reforms the starting six-coordinated low spin iron(III) porphyrin.

The discovery of the so-called 'peroxide shunt' pathway, which is the direct formation of the high-valent iron(V)-oxo species **1.31** by external oxidizing agents such as iodosylbenzene, peracids, or hypochlorite, led to the design of several biomimetic metallo-porphyrin catalysts.

Chiral porphyrins[12] are usually prepared either by attaching chiral units to the preformed amino- or hydroxy-substituted porphyrins or by condensation of chiral aldehydes with pyrrole. In the ligand, the chiral units form pickets or straps connecting diagonal or adjacent meso centers. We can make difference between single and

[12] a. Collman J. P.; Zhang X.; Lee V. J.; Uffelman E. S.; Brauman J. I. *Science* **1993**, *261*, 1404; b. Rose E.; Andrioletti B.; Zring S.; Quelquejeu-Ethève M. *Chem. Soc. Rev.* **2005**, *34*, 573

double faced porphyrins regarding the position of the chiral units in the molecule.

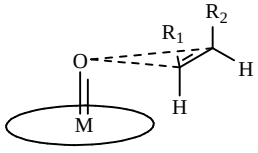


Schematic drawing of single faced picket and strapped porphyrin examples

Scheme 16

A high number of chiral porphyrin structures have been synthesized but only few of them were successful in enantioselective epoxidation catalysis. Manganese and iron derivatives became the most common metalloporphyrin oxidizing catalysts.

Regarding the substrate scope, *cis* di-substituted and terminal alkenes are good substrates for porphyrin-mediated asymmetric epoxidation. Based on the observation that *cis* alkenes react faster than *trans* alkenes and that 1,1-disubstituted alkenes show similar reactivities to *trans* 1,2-disubstituted double bonds, Groves and Nemo proposed that the double bond of the olefin approaches from the side to the metal-oxo bond and parallel to the porphyrin plane (*Scheme 17*).[13] Such a side-on approach could maximize the interaction between the alkene π orbitals and the metal-oxo π non-bonding orbitals.

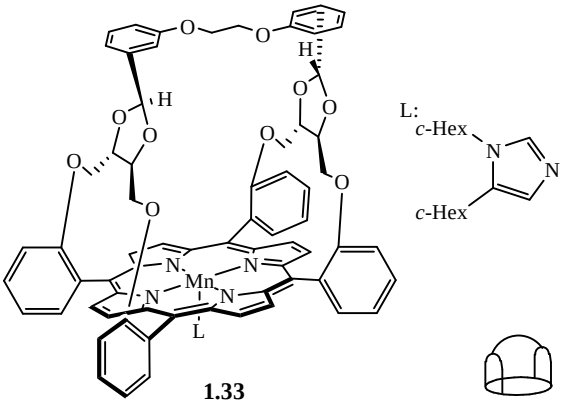


1.32

Scheme 17

[13] Groves J. T.; Nemo T. E. *J. Am. Chem. Soc.* **1983**, *105*, 5786

In the case of single faced porphyrins, the achiral open face has to be blocked by a strongly coordinating ligand to obtain high enantioselectivities in the oxidation. Additionally, this ligand has to be bulky enough to avoid its coordination in the chiral cavity. As an example, Collman *et al*. achieved up to *88%* ee for *cis*-disubstituted alkenes and up to *79%* ee for monosubstituted olefins with their threitol strapped manganese porphyrin system, using 1,5-dicyclohexyl imidazole as ligand (*Scheme 18*).[14] Using smaller ligands, the ee drops dramatically.

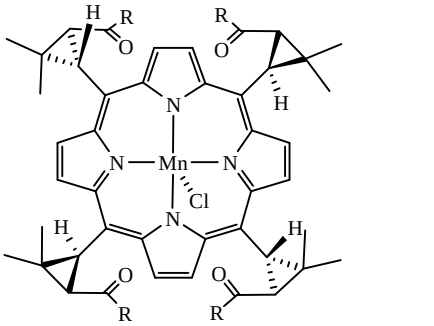


1.33

Scheme 18

Among the double face picket porphyrins, remarkable results were obtained using chiroporphyrin **1.34** described by Marchon *et al*. (*Scheme 19*).[15] Up to *86%* ee was obtained for the epoxidation of 1,2-dihydronaphthalene using the manganese complex of this bulky ligand.

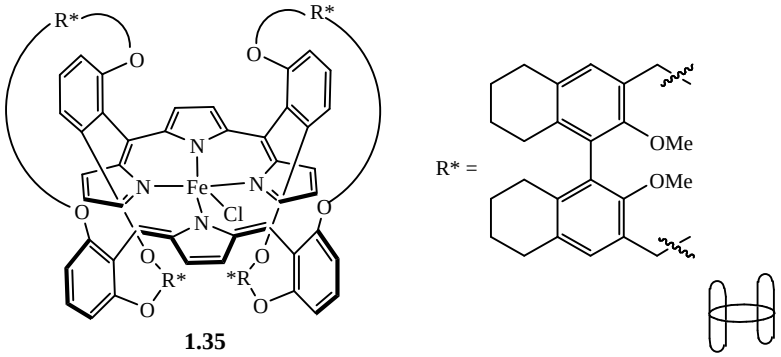
[14] Collman J. P.; Lee V. J.; Kellen-Yuen C. J.; Zhang X.; Ibers J. A.; Brauman J. I. *J. Am. Chem. Soc.* **1995**, *117*, 692
[15] Pérollier C.; Pécaut J.; Ramasseul R.; Marchon J. C. *Inorg. Chem.* **1999**, *38*, 3758



1.34

Scheme 19

The iron complex of double face strapped 'twin coronet' porphyrin **1.35** presented by Naruta *et al*. gives only moderate enantioselectivity in the epoxidation of styrene, but high enantiomeric excess for electron deficient substrates such as 2-nitrostyrene (*89%* ee). [16]



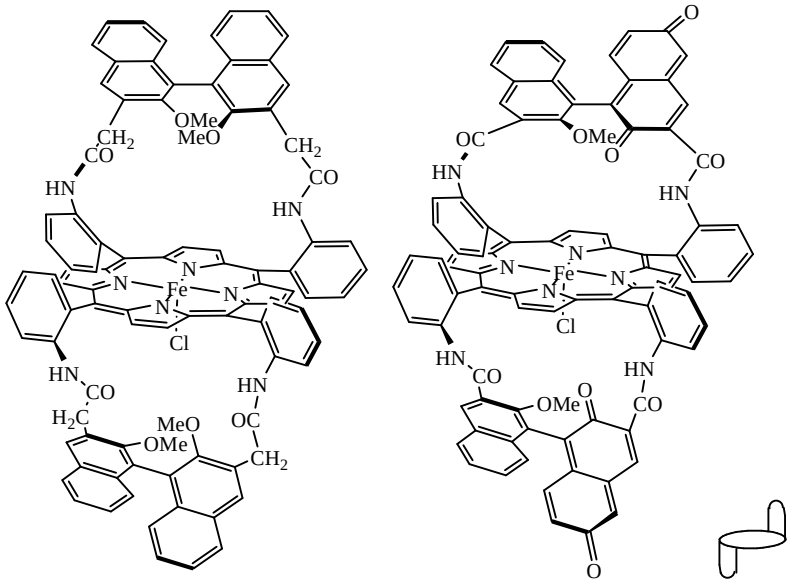
1.35

Scheme 20

Probably the best porhphyrin catalyst described up to now for the asymmetric epoxidation of terminal olefins is **1.36**, the binaphthyl

[16] a. Naruta Y.; Ishihara N.; Tani F.; Maruyama K. *Chem. Lett.* **1991**, 1933; b. Naruta Y.; Tani F.; Ishihara N.; Maruyama K. *J. Am. Chem. Soc.* **1991**, *113*, 6865

strapped iron-porphyrin of Rose *et al.* (*Scheme 21*).[17] This robust, recoverable, and reusable catalyst provides terminal epoxides in high yield and excellent ee (up to *97%*).



1.36 **1.37**

Scheme 21

It has to be mentioned that, when the strap is two methylene units shorter, the methoxy groups became too close to the metal center and they are oxidized.[18] The formation of quinone is such an important structural change that the modified ligand provides the opposite enantiomer preferentially. The difficulty of designing suitable ligands is clearly apparent in this example. The chirality has to be close enough to the site of oxidation to induce asymmetry, but far enough to avoid degradation.

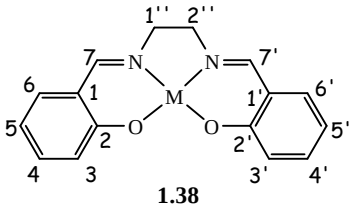
[17] Rose E.; Ren Q-Z.; Andrioletti B. *Chem. Eur. J.* **2004**, *10*, 224

[18] a. Collman J. P.; Wang Z.; Straumanis A.; Quelquejeu M. *J. Am. Chem. Soc.* **1999**, *121*, 460; b. Rose E.; Quelquejeu M.; Padian R. P.; Lecas-Nawrocka A.; Vilar A.; Ricart G.; Collman J. P.; Wang Z.; Straumanis A. *Polyhedron* **2000**, *19*, 581

As we can see, all of the highly enantioselective porphyrin catalysts are limited to a very narrow range of alkenes.

I. 4. Metal-salen complexes

In 1990, Jacobsen[19] and Katsuki[20] almost simultaneously published the success of chiral manganese-salen complexes as asymmetric epoxidation catalysts. Inspired by the work of Kochi[21] on the epoxidation of olefins using metal salen complexes, they discovered the potency of this C_2 symmetric tetradentate ligand. Modifying the structure by placing stereogenic centers at C-1'' and C-2'' and bulky and/or chiral substituents at C-3 and C-3', they achieved moderate to good enantioselectivities for the epoxidation of unfunctionalized alkenes using iodosylbenzene as stoichiometric oxidant.



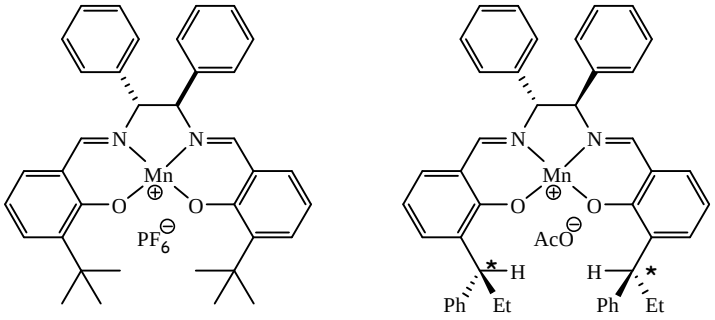
1.38

Scheme 22

The main difference between their systems is that Jacobsen used bulky *t*-butyl groups at the C-3 and C-3' positions, whilst Katsuki placed new stereogenic centers there (*Scheme 23*). These additional chirality elements led to the formation of matched and

[19] Zhang W.; Loebach J. L.; Wilson S. R.; Jacobsen E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801
[20] Irie R.; Noda K.; Ito Y.; Matsumoto N.; Katsuki T. *Tetrahedron Lett.* **1990**, *31(50)*, 7345
[21] Srinivasan K.; Michaud P.; Kochi J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309

mismatched pairs. The combination of the (*R*, *R*) diamine moiety with the substituent having *S* absolute configuration resulted in higher asymmetric induction than with the corresponding *R* one.



1.39 **1.40**

Scheme 23

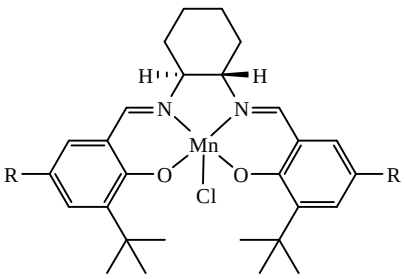
Since these pioneering publications, numerous modifications of the original Mn-salen catalysts have been made and improved enantioselectivities have been reached.[22] The straightforward synthesis of salen ligands from readily available chiral diamines and easily functionalized salicylaldehyde derivatives provided a fast development of this field.

Jacobsen revealed the importance of a bulky substituent at the C-5 and C-5' positions to narrow further the possible trajectory of the incoming olefin. Additionally, he demonstrated the beneficial influence of electron donating substituents on the enantioselectivity. His finest catalysts are presented in *Scheme 24*.[23] Meantime, Katsuki introduced axial chirality at the C-3 and C-3' positions in his second

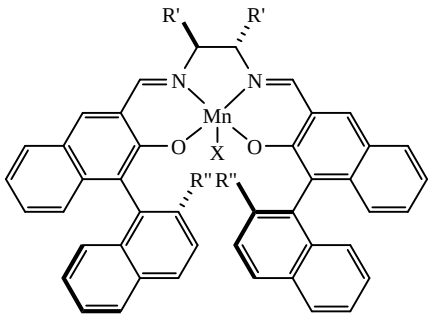
[22] Reviews: a. Katsuki T. *Coord. Chem. Rev.* **1995**, *140*, 189; b. Katsuki T. *J. Mol. Catal. A: Chem.* **1996**, *113*, 87; c. Canali L.; Sherrington D. C. *Chem. Soc. Rev.* **1999**, *28*, 85; d. McGarrigle E. M.; Gilheany D. G. *Chem. Rev.* **2005**, *105(5)*, 1563

[23] a. Jacobsen E. N.; Zhang W.; Muci A. R.; Ecker J. R.; Deng L. *J. Am. Chem. Soc.* **1991**, *113*, 7063; b. Brandes B. D.; Jacobsen E. N. *J. Org. Chem.* **1994**, *59*, 4378

generation catalysts, obtaining the general structure **1.43** depicted below.[24] He concluded from the experimental results, that enantiofacial selection of *cis*-olefins is preferentially controlled by the chirality at C-1'' and C-2'', and that of *trans*-olefins by the chirality of the C-3 and C-3' substituents.[25]



1.41 R= *t*-Bu
1.42 R= OSi(*i*-Pr)$_3$



1.43

Scheme 24

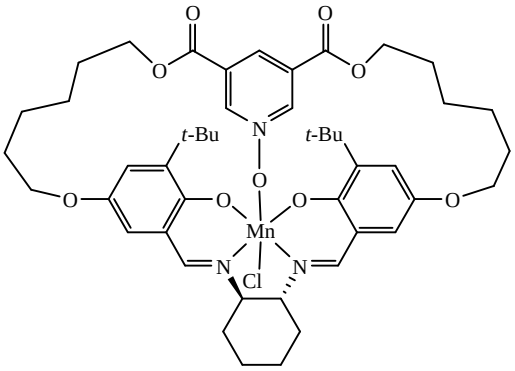
In addition to manganese, the salen complexes of various other metal ions, such as chromium, nickel and ruthenium have been tested as epoxidation catalysts. Moreover, besides iodosylbenzene, a variety of other terminal oxidizing agents were used, such as, aqueous sodium hypochlorite, hydrogen peroxide, molecular oxygen in the presence of an aldehyde, and peracids.

The influence of various nitrogen and oxygen donor ligands, as well as different counterions, on the yield and enantioselectivity of the reaction has been studied in detail. It has been concluded that these additives increase the yield by blocking the formation of unreactive μ-oxo Mn(IV) dimers. Additionally, the donor ligand decreases the

[24] Sasaki H.; Irie R.; Katsuki T. *Synlett* **1994**, 356
[25] a. Irie R.; Noda K.; Ito Y.; Matsumoto N.; Katsuki T. *Tetrahedron: Asymmetry* **1991**, *2(7)*, 481; b. Irie R.; Noda K.; Ito Y.; Katsuki T. *Tetrahedron Lett.* **1991**, *32(8)*, 1055; c. Hosoya N.; Irie R.; Katsuki T. *Synlett* **1993**, 261

Lewis acidity of the metal center and thus increased the yield by avoiding the formation of ring-opened side products. The coordination of these axial ligands changes the conformation of the active oxidizing species. In most of the cases, this conformational change is advantageous for the optical purity. However, in some cases, the optimal conformation has already been achieved before ligand coordination, and the additive decreases the enantioselectivity of the reaction.[26]

To demonstrate the importance of additives, Jacobsen synthesized and tested complex **1.44** in which the axial ligand is already part of the complex structure (*Scheme 25*).[27] The results, obtained using this catalyst, are not modified by the presence of donor additives.



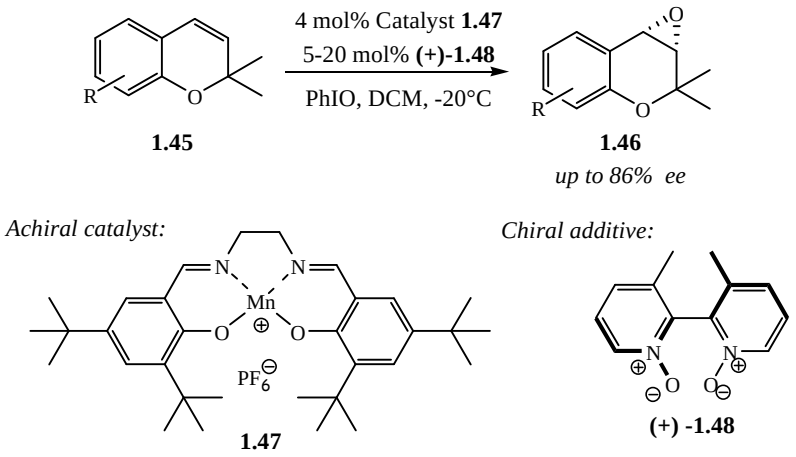
1.44

Scheme 25

Observing the great influence of additive donor ligands, Katsuki proposed the use of achiral salen complex in the presence of

[26] Ryan K. M.; Bousquet C.; Gilheany D. G. *Tetrahedron Lett.* **1999**, *40*, 3613
[27] Finney N. S.; Pospisil P. J.; Chang S.; Palucki M.; Konsler R. G.; Hansen K. B.; Jacobsen E. N. *Angew. Chem. Int. Ed. Engl.* **1997**, *36(16)*, 1720

chiral additives for asymmetric induction.[28] By this method, he performed the epoxidation of chromene derivatives in moderate to good yields and up to *86%* enantiomeric excess, using the achiral complex **1.47** as catalyst in the presence of enantiopure (+)-3,3'-dimethyl-2,2'-bipyridine *N,N'*-dioxide **1.48** as chiral additive (*Scheme 26*).



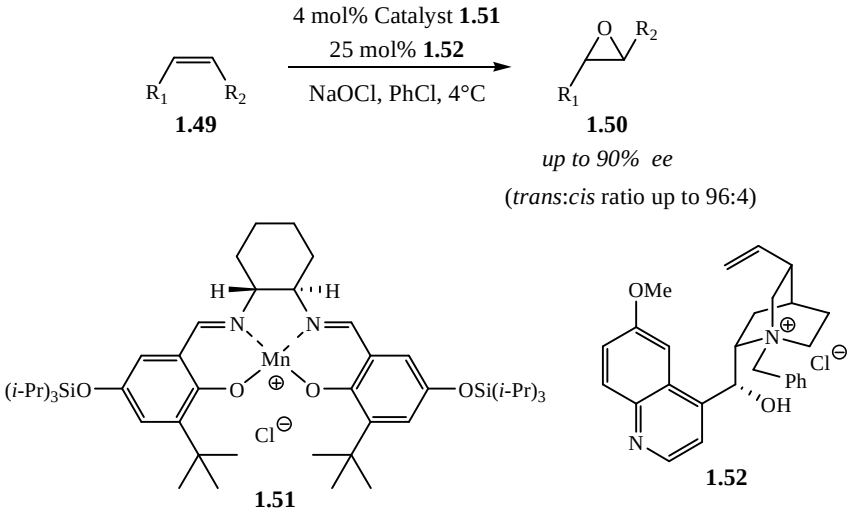
Scheme 26

In general, metallosalens are considered effective catalysts for the asymmetric epoxidation of conjugated *cis*-di-, tri-, and some tetra-substituted olefins. Up to *>99%* enantiomeric excess has been achieved for those substrates. Highly enantioselective epoxidation of conjugated mono-substituted olefins requires special, low temperature conditions.[29] Compared to conjugated substrates, simple alkenes give usually low enantioselectivities. *Trans*-alkenes are generally poor

[28] a. Hashihayata T.; Ito Y.; Katsuki T. *Synlett* **1996**, 1079; b. Hashihayata T.; Ito Y.; Katsuki T. *Tetrahedron* **1997**, *53(28)*, 9541; c. Miura K.; Katsuki T. *Synlett* **1999**, *6*, 783

[29] a. Palucki M.; Pospisil P. J.; Zhang W.; Jacobsen E. N. *J. Am. Chem. Soc.* **1994**, *116*, 9333; b. Palucki M.; McCormick G. J.; Jacobsen E. N. *Tetrahedron Lett.* **1995**, *36(31)*, 5457

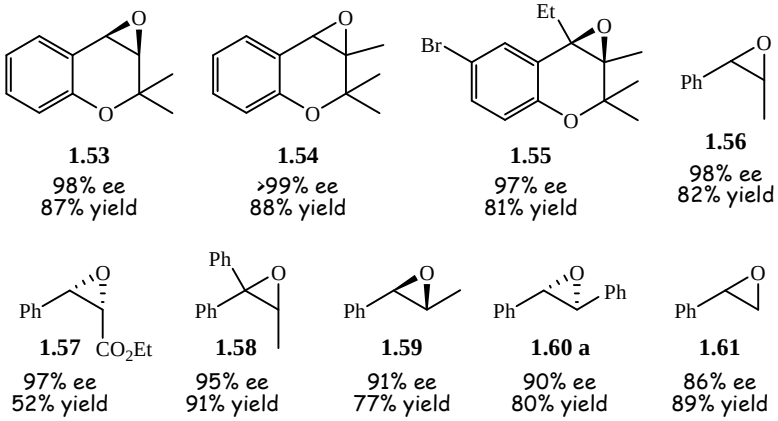
substrates for metallosalen catalysis. Only a few examples can be found in literature in which *trans*-alkenes are epoxidized in around *90%* enantiomeric excess.[30] An alternative method to obtain *trans*-epoxides with good selectivity has been reported by Jacobsen.[31] Using cinchona alkaloid derivatives as additives in the epoxidation of *cis*-alkenes, he obtained the corresponding *trans*-epoxides with up to *90%* enantiomeric excess and good to excellent diastereoselectivity (*Scheme 27*).



Scheme 27

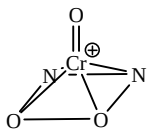
Thus, fine-tuning of the salen catalysts and of the reaction conditions led to the obtention of high asymmetric induction for a relatively large number of substrates. Concrete examples of the most successful results obtained using the different salen complexes are shown below.

[30] a. Nishikori H.; Ohta C.; Katsuki T. *Synlett* **2000**, *11*, 1557; b. Daly A. M.; Renehan M. F.; Gilheany D. G. *Org. Lett.* **2001**, *3(5)*, 663
[31] Chang S.; Galvin J. M.; Jacobsen E. N. *J. Am. Chem. Soc.* **1994**, *116*, 6937



Scheme 28

Despite the rapid expansion of its substrate scope and the excellent enantioselectivity levels observed, the mechanism of the asymmetric metallosalen epoxidation is still being questioned. It is generally agreed that, similarly to the porphyrin systems, the initial complex is oxidized to a reactive metal-oxo intermediate. Mn(V)=O salen complexes haven't been isolated yet, but the existence of analogous cationic Cr(V)=O complexes has been confirmed by X-ray crystallographic analysis.[32] The oxochromium(V)salen complex has a roughly square pyramidal coordination in which the chromium atom is 0.53 Å above the salen plane (*Scheme 29*). It has been also revealed that, when pyridine *N*-oxide is coordinated as an axial ligand, the distance between the chromium atom and the plane deceases to 0.26 Å.

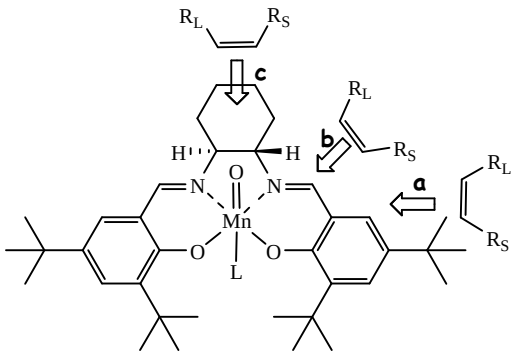


1.62

Scheme 29

[32] Samsel E. G.; Srinivasan K.; Kochi J. K. *J. Am. Chem. Soc.* **1985**, *107*, 7606

The side-on approach of the olefin to the metal-oxo bond, described previously for porphyrin systems, is generally considered appropriate for the structurally similar salen complexes. Three different pathways have been proposed for the incoming olefin (*Scheme 30*).

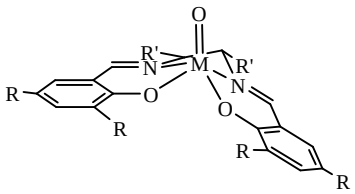


1.63

Scheme 30

For the first catalysts, pathway **a** has been suggested, in which the olefin approaches between the nitrogen and the oxygen atoms, orienting the bulkier substituents away from the C-3 and C-3' substituents to avoid steric repulsions. However, this approach is not suitable when bulky substituents are present at C-5 and C-5'. For those complexes, Jacobsen proposes pathway **c**; that is, attack from the direction of the diimine bridge, placing the smaller substituent of the olefin on the same side as the axial hydrogen atom of the chiral center. Alternatively, Katsuki suggests pathway **b** for his second generation catalysts, taking into consideration not only steric, but also π-electronic repulsions. On the other hand, he also emphasizes that the upper proposals are all based on the hypothesis that the reactive oxo species enjoys a planar structure. Pointing to the observed, slightly folded structure of oxochromium(V)salen complexes (*Scheme 31*),

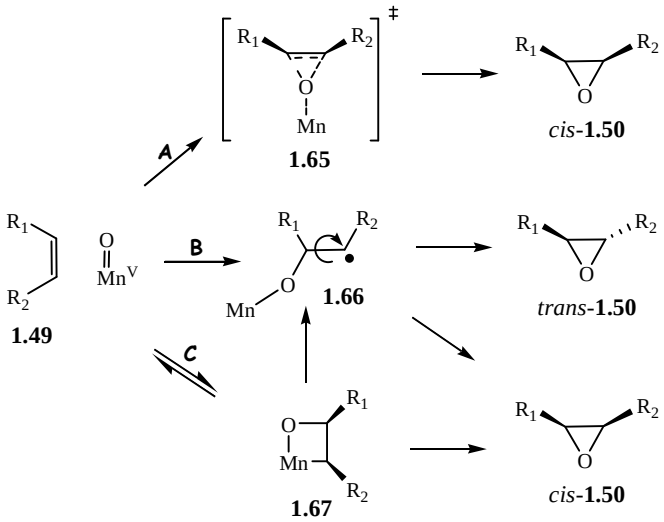
Katsuki envisaged the possibility of pathway **a** even in the presence of bulky C-5 and C-5' substituents. Gilheany explains similarly his remarkable results obtained for *trans* alkenes in chromium salen catalyzed epoxidation.[33]



1.64

Scheme 31

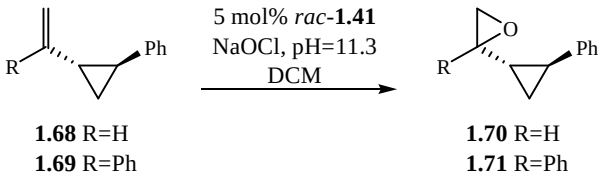
The most plausible mechanisms for oxygen transfer to the double bond are concerted (**A**), stepwise *via* radical intermediates (**B**), and [2+2] cycloaddition, forming a metallaoxetane intermediate (**C**) (*Scheme 32*).[34]



Scheme 32

[33] a. Ryan K. M.; Bousquet C.; Gilheany D. G. *Tetrahedron Lett.* **1999**, *40*, 3613; b. Daly A. M.; Renehan M. F.; Gilheany D. G. *Org. Lett.* **2001**, *3(5)*, 663
[34] Linker T. *Angew. Chem. Int. Ed. Engl.* **1997**, *36(19)*, 2060

Conjugated *cis* olefins often give mixtures of *cis* and *trans* epoxides, while non-conjugated *cis* olefins afford stereoselectively the *cis* products. Based on these observations, the concerted pathway **A** has been proposed for the epoxidation of simple alkenes and the stepwise, radical pathway **B**, with possibility of rotation around the C-C single bond, has been suggested for the oxidation of conjugated alkenes. Jacobsen supported the non-radical pathway by the observation that the epoxidation of *trans*-2-phenyl-1-vinylcyclopropene **1.68** did not led to the opening of the cyclopropene ring.[35] More interestingly, the conjugated derivatives, such as **1.69**, can also be epoxidized under certain conditions without ring opening (*Scheme 33*).[36]



1.68 R=H
1.69 R=Ph

1.70 R=H
1.71 R=Ph

Scheme 33

Based on the observation of non-linear correlation between asymmetric induction and temperature in case of certain substrates, Katsuki proposed the reversible formation of several intermediates.[37] Accordingly, he suggested the formation of metallaoxetane species (pathway **C**). Jacobsen, however, questions these results since he always found a linear correlation between asymmetric induction and

[35] Fu H.; Look G. C.; Zhang W.; Jacobsen E. N.; Wong C.-H. *J. Org. Chem.* **1991**, *56*, 6497
[36] Linde C.; Arnold M.; Norrby P.-O.; Åkermark B. *Angew. Chem. Int. Ed. Engl.* **1997**, *36(16)*, 1723
[37] a. Hamada T.; Fukuda T.; Imanishi H.; Katsuki T. *Tetrahedron* **1996**, *52(2)*, 515; b. Katsuki T. *J. Synth. Org. Chem. Jpn.* **1995**, *53(11)*, 940

temperature using his own catalysts.[38] The two investigations were conducted, not only with different catalysts, but also under different conditions.

Analyzing these results, it is becoming more and more evident that, for the same substrate, radical and non-radical pathways are in competition and that the reaction conditions play a fundamental role in the partition of these different pathways.

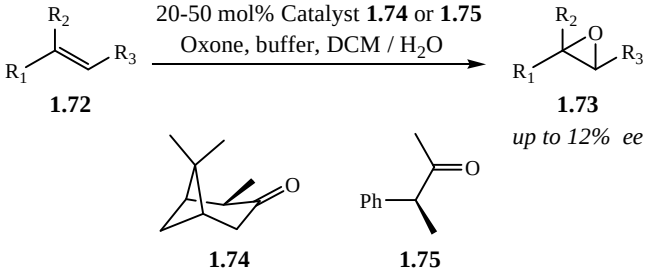
The introduction of optically active salen complexes provided a major leap in the asymmetric epoxidation of unfunctionalized olefins. At the present time, among all the published organometallic catalysts, the best enantiomeric excesses for the widest range of olefins are obtained by chiral salen complexes. The enormous success of salen complexes, compared to the porphyrin systems, originates from the possibility to place the chirality closer to the site of oxidation. The success of the most generally used Jacobsen's catalyst lays also in its straightforward synthesis.[39] The second generation manganese-salen catalysts introduced by Katsuki and co-workers have surpassed Jacobsen's catalyst in terms of selectivity and activity, but they are not as synthetically accessible and this limits their application.

I. 5. Chiral ketone catalysts

In 1984, Curci and co-workers reported the first, chiral ketone catalyzed asymmetric epoxidation reaction.[40] Using (+)-isopinocam-

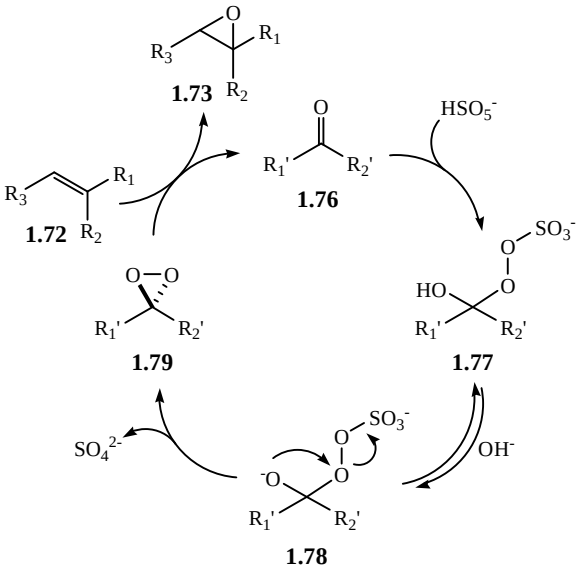
[38] Finney N. S.; Pospisil P. J.; Chang S.; Palucki M.; Konsler R. G.; Hansen K. B.; Jacobsen E. N. *Angew. Chem. Int. Ed. Engl.* **1997**, *36(16)*, 1720
[39] Larrow J. F. ; Jacobsen E. N. *J. Org. Chem.* **1994**, *59*, 1939
[40] Curci R.; Fiorentino M.; Serio M. R. *J. Chem. Soc., Chem. Commun.* **1984**, 155

phone **1.74** or (*S*)-(+)-3-phenylbutan-2-one **1.75** as catalyst, he obtained epoxides in good yield and modest enantioselectivity (*Scheme 34*).



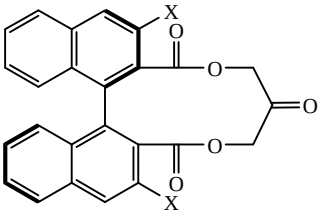
Scheme 34

In this reaction, Oxone (a 2:1:1 mixture of $KHSO_5$, $KHSO_4$ and K_2SO_4) is used as the stoichiometric oxidant and the chiral dioxirane, generated *in situ* from the ketone, performs the epoxidation. As can be seen in the proposed catalytic cycle presented in *Scheme 35*, the ketone is regenerated after the epoxidation step. Therefore, it can be used in catalytic quantities.



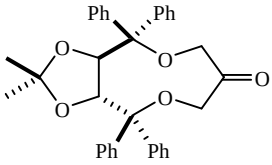
Scheme 35

During the past few years, various chiral ketones have been tested as catalysts by several research groups.[41] Among them, we have to mention Yang's binaphthalene derived ketones, Adam's Taddol derived ketones, Armstrong's bicyclo-ketones, Denmark's fluoro-ketones and Shing's arabinose derived ketones (*Scheme 36*).[42]

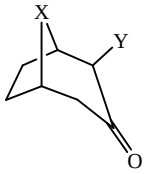


X = H, Cl, Br, CH($OCH_2CH_2CH_2O$)

1.80 Yang

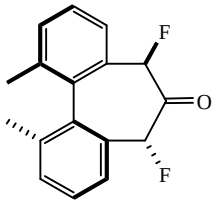


1.81 Adam

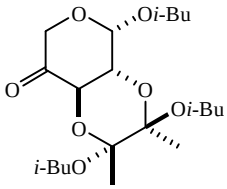


X = O, NCO_2Et
Y = F, OAc

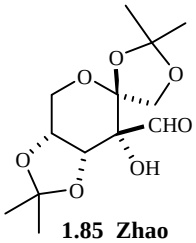
1.82 Armstrong



1.83 Denmark



1.84 Shing



1.85 Zhao

Scheme 36

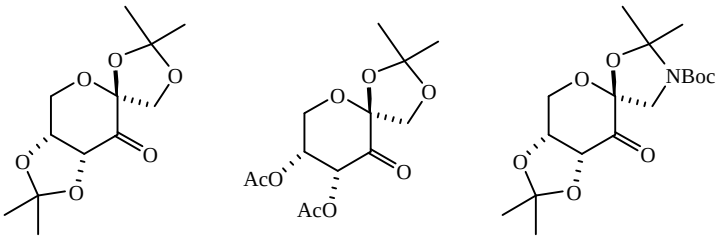
[41] Reviews: a. Yang D. *Acc. Chem. Res.* **2004**, *37*, 497; b. Wong A. O. ; Shi Y. *Chem. Rev.* **2008**, *108(9)*, 3958

[42] a. Yang D.; Yip Y-C.; Tang M-W.; Wong M-K.; Zheng J-H.; Cheung K-K. *J. Am. Chem. Soc.* **1996**, *118*, 491; Yang D.; Wang X-C.; Wong M-K.; Yip Y-C.; Tang M-W. *J. Am. Chem. Soc.***1996**, *118*, 11311; Yang D.; Wong M-K.; Yip Y-C.; Wang X-C.; Tang M-W.; Zheng J-H.; Cheung K-K. *J. Am. Chem. Soc.* **1998**, *120*, 5943; b. Adam W.; Zhao C-G. *Tetrahedron: Asymmetry* **1997**, *8(24)*, 3995; c. Armstrong A.; Hayter B. R. *Chem. Commun.* **1998**, 621; Armstrong A.; Hayter B. R.; Moss W. O.; Reeves J. R.; Wailes J. S. *Tetrahedron: Asymmetry* **2000**, *11*, 2057; Armstrong A.; Moss W. O.; Reeves J. R. *Tetrahedron: Asymmetry* **2001**, *12*, 2779; Armstrong A.; Ahmed G.; Dominguez-Fernandez B.; Hayter B. R.; Wailes J. S. *J.Org. Chem.* **2002**, *67*, 8610; d. Denmark S. E.; Wu Z.; Crudden C. M.; Matsuhashi H. *J. Org. Chem.* **1997**, *62*, 8288; Denmark S. E.; Wu Z. *Synlett*, **1999**, 847; Denmark S. E.; Matsuhashi H. *J. Org. Chem.* **2002**, *67*, 3479; e. Shing T. K. M.; Leung G. Y. C.; Yeung K. W. *Tetrahedron Lett.* **2003**, *44*, 9225; Shing T. K. M.; Leung G. Y. C.; Luk T. *J. Org. Chem.* **2005**, *70*, 7279

Additionally, Zhao reported that optically active aldehydes such as **1.85**, could be promising asymmetric epoxidation catalysts.[43]

Although encouraging results were obtained with the above mentioned ketones, the observed enantioselectivities were quite substrate dependent, giving excellent results only for *trans*-stilbene or phenylstilbene derivatives.

The real breakthrough in ketone catalysis in the field of asymmetric epoxidation is attributable to Shi and co-workers. In 1996, he reported **1.86**, a fructose derived ketone, as a highly reactive and enantioselective catalyst for the epoxidation of *trans*- and trisubstituted olefins.[44]



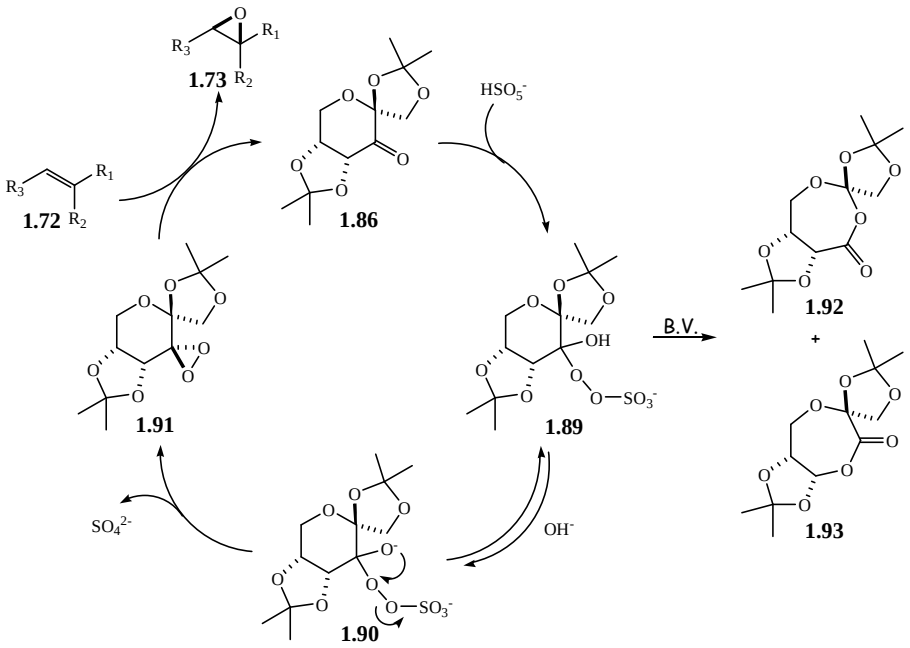
1.86 **1.87** **1.88**

Scheme 37

The success of this catalyst results from several structural parameters. A fused ring and a quaternary centre are used to minimize the potential epimerisation of the stereogenic centres next to the reacting carbonyl. The adjacent position of these chiral centres to the active site is advantageous for the stereochemical interactions between substrate and catalyst. Additionally, the electron-withdrawing groups inductively activate the carbonyl function.

[43] Bez G.; Zhao C-G. *Tetrahedron Lett.* **2003**, *44*, 7403
[44] Tu Y.; Wang Z.-X.; Shi Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806

A careful control of the pH is required during the reaction. Usually, epoxidations with *in situ* generated dioxiranes are carried out at pH 7-8, since higher pH leads to the rapid autodecomposition of Oxone. At this pH, however, ketone **1.86** decomposes *via* Baeyer-Villiger oxidation (*Scheme 38*). Therefore, a large amount of ketone is necessary in order to obtain satisfactory yields of epoxide. By increasing the pH to 10.5, the Baeyer-Villiger oxidation is overridden and the epoxidation can be carried out with catalytic amounts of ketone. Moreover, at this pH, the ketone is sufficiently reactive to compete with the decomposition of Oxone, and thus, the amount of Oxone can be reduced considerably as well.



Scheme 38

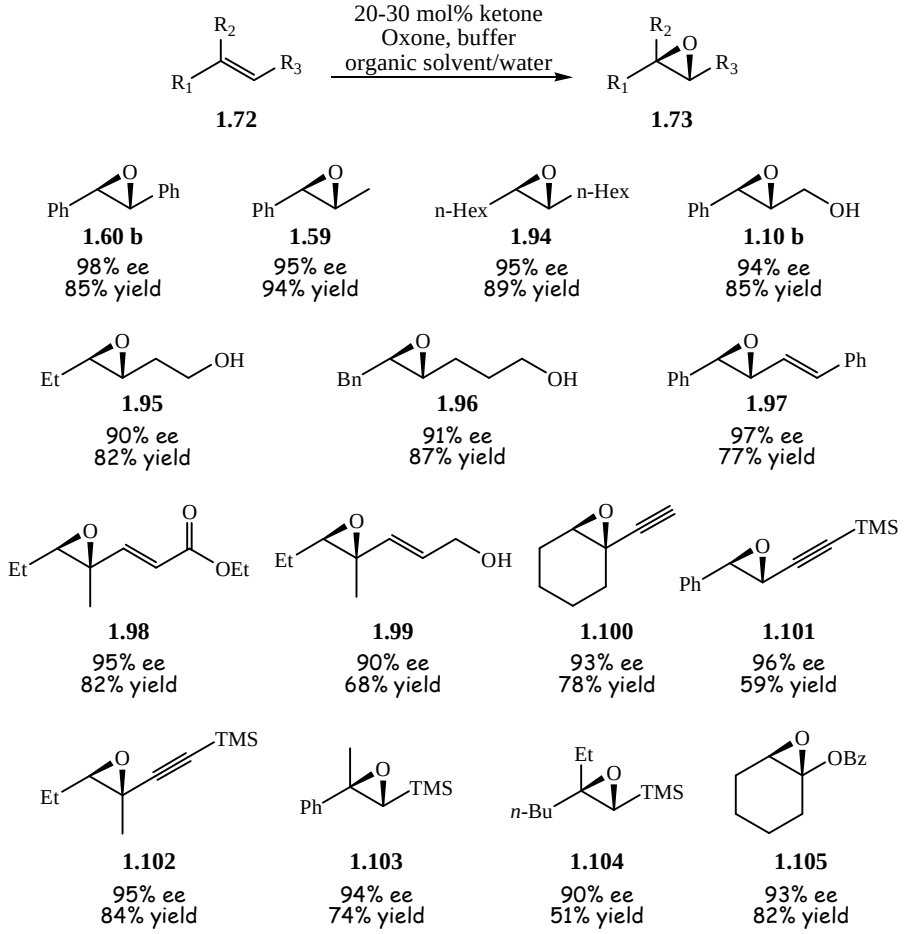
Oxone is almost exclusively used as the oxidant in ketone-mediated epoxidations. However, peroxyimidic acids, generated from hydrogen peroxide and a nitrile, proved to be also suitable oxidants.[45]

The scope and limitations of catalyst **1.86** have been extensively investigated. Good yields and high enantioselectivities can be obtained for a variety of unfunctionalized *trans*- and trisubstituted olefins. The *95%* enantiomeric excess obtained in the epoxidation of *trans*-7-tetradecene demonstrates the general applicability of the system for simple *trans* olefins.[46] On the other hand, *cis*-disubstituted and terminal alkenes are rather poor substrates.

As can be seen in *Scheme 39*, among the t*rans*- and trisubstituted olefins, hydroxyalkenes, such as, allylic, homoallylic and bishomoallylic alcohols are smoothly oxidized.[47] Monoepoxidation of conjugated dienes favors the more electron-rich and less sterically hindered olefin.[48] Enynes are efficiently oxidized to propargylic epoxides.[49] 2,2-Disubstituted vinyl silanes can be epoxidized with high enantioselectivities, giving access to disubstituted terminal epoxides upon desilylation.[50] Furthermore, enol esters can be enantioselectively epoxidized by this method.[51]

---

[45] a. Shu L.; Shi Y. *Tetrahedron Lett.* **1999**, *40*, 8721; b. Shu L.; Shi Y. *Tetrahedron* **2001**, *57*, 5213
[46] Wang Z.-X.; Tu Y.; Frohn M.; Zhang J.-R.; Shi Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224
[47] Wang Z.-X.; Shi Y. *J. Org. Chem.* **1998**, *63*, 3099
[48] Frohn M.; Dalkiewicz M.; Tu Y.; Wang Z.-X.; Shi Y. *J. Org. Chem.* **1998**, *63*, 2948
[49] a. Cao G.-A.; Wang Z.-X.; Tu Y.; Shi Y. *Tetrahedron Lett.* **1998**, *39*, 4425; b. Wang Z.-X.; Cao G.-A.; Shi Y. *J. Org. Chem.* **1999**, *64*, 7646
[50] Warren J. D.; Shi Y. *J. Org .Chem.* **1999**, *64*, 7675
[51] a. Zhu Y.; Tu Y.; Yu H.; Shi Y. *Tetrahedron Lett.* **1998**, *39*, 7819; b. Zhu Y.; Shu L.; Tu Y.; Shi Y. *J. Org. Chem.* **2001**, *66*, 1818

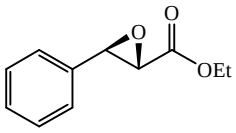


Scheme 39

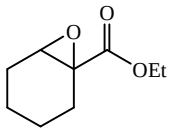
Several structural modifications of the catalyst have been tested to improve further the obtained results.[52] Up to now, none of the modified ketone can compete with catalyst **1.86** for the epoxidation of *trans*- and trisubstituted olefins. However, a few of them draw the attention of the researchers by their promising selectivity and activity towards other types of olefins.

[52] a. Tu Y.; Wang Z.-X.; Frohn M.; He M.; Yu H.; Tang Y.; Shi Y. *J. Org. Chem.* **1998**, *63*, 8475; b. Wang Z.-X.; Miller S. M.; Anderson O. P.; Shi Y. *J. Org. Chem.* **1999**, *64*, 6443; c. Tian H.; She X.; Shi Y. *Org. Lett.* **2001**, *3(5)*, 715; d. Wang Z.-X.; Miller S. M.; Anderson O. P.; Shi Y. *J. Org. Chem.* **2001**, *66*, 521; e. Shu L.; Shi Y. *Tetrahedron Lett.* **2004**, *45*, 8115; f. Shi Y. *Acc. Chem. Res.* **2004**, *37*, 488

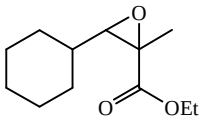
The original Shi catalyst reacts sluggishly with electron deficient *α,β*-unsaturated esters, and the prolonged reaction times result in the decomposition of the catalyst *via* the Baeyer-Villiger pathway. Contrary to **1.86**, the more robust ketone **1.87** was found to be efficient in the epoxidation of such electron deficient substrates.[53] High ee's and good yields were obtained for *trans*-cinnamates and trisubstituted *α,β*-unsaturated esters (*Scheme 40*). However, low ee's were obtained for *cis*-cinnamate, and the catalyst is not effective towards *trans*-aliphatic *α,β*-unsaturated esters.



1.106 a
96% ee
73% yield



1.107
93% ee
77% yield

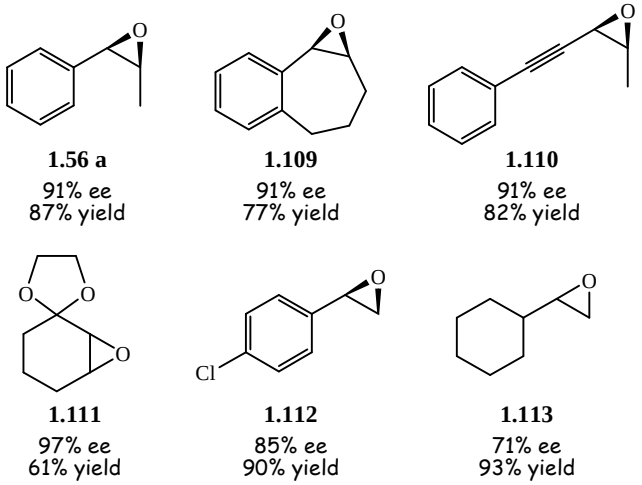


1.108
89% ee
77% yield

Scheme 40

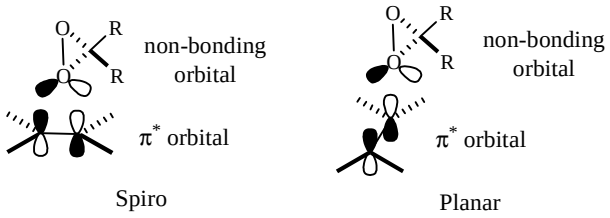
Glucose derived ketone **1.88** was reported as a highly enantioselective catalyst for the epoxidation of several *cis*-disubstituted olefins.[54] The enantiomeric excess is generally high for *cis*-alkenes conjugated with an aromatic ring or an alkynyl group. Importantly, no isomerization was observed in the epoxidation of acyclic systems. Additionally, encouragingly high ee's were obtained for certain terminal olefins.[55] Some selected examples of the substrate scope are collected in *Scheme 41*.

[53] Wu X.-Y.; She X.; Shi Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792
[54] a. Tian H.; She X.; Shu L.; Yu H.; Shi Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551; b. Tian H.; She X.; Yu H.; Shu L.; Shi Y. *J. Org. Chem.* **2002**, *67*, 2435
[55] Tian H.; She X.; Xu J.; Shi Y. *Org. Lett.* **2001**, *3(12)*, 1929



Scheme 41

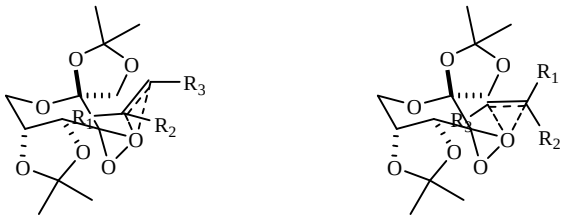
Great efforts have been made to rationalize the observed stereochemical outcome of Shi's epoxidation system. From the two diastereomeric oxygen of the dioxirane intermediate, the sterically more accessible equatorial oxygen is likely to be transferred onto the olefin. For this oxygen transfer, competing spiro and planar transition state geometries have been proposed (*Scheme 42*). Between these two extreme geometries, the spiro transition state is believed to be electronically favoured, due to the stabilizing interactions of an oxygen lone pair and the π^* orbital of the olefin.



Scheme 42

It is stated that, in the epoxidation of *trans*- and trisubstituted olefins with catalyst **1.86**, planar transition state **B** competes with the favored spiro geometry **A** (*Scheme 43*). The electronic and steric

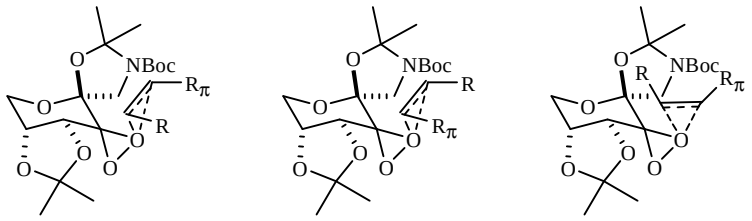
features of the olefin substituents can modify the participation of these competing transition states, hence influencing the enantioselectivity of the reaction. Conjugating substituents, such as aromatic rings, alkenyl or alkynyl groups, generally increase the enantioselectivity. Indeed, the conjugation lowers the energy of the π^* orbital of the double bond, and the participation of the spiro transition state increases further due to the increasing stabilizing interaction. Concerning the steric parameters, smaller R_1 and larger R_3 substituents are beneficial to the optical purity of the product epoxide. While a smaller R_1 is advantageous for spiro **A**, a larger R_3 is disadvantageous for planar transition state **B**.



Spiro **A** (favoured) Planar **B**

Scheme 43

Concerning the epoxidation of *cis*-disubstituted and terminal olefins with ketone **1.88**, it is found from the absolute configuration of several epoxides that the π-substituent of the substrate prefers to be proximal to the spiro oxazolidinone. Thus, spiro **C** is favoured over spiro **D** transition state (*Scheme 44*). In the case of *cis*-olefins, spiro **C** and **D** are the two most plausible transition states. For terminal olefins, however, planar **E** can also be considered as a plausible candidate. The multiplicity of energetically close transition states explains the lower enantioselectivities obtained for terminal olefins.



Spiro **C** (favoured) Spiro **D** Planar **E**

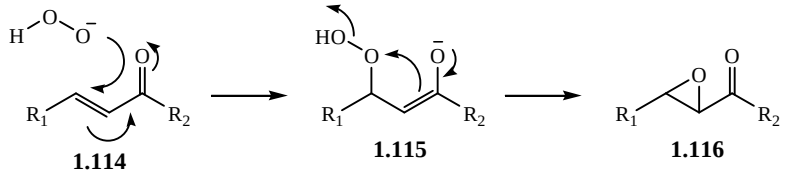
Scheme 44

Rationalizing the stereochemical outcome of these epoxidations by transition state models will probably help the future development of even more selective ketone catalysts. Anyway, due to the impressive results obtained by Shi, dioxirane-mediated epoxidation became already one of the most efficient catalytic asymmetric epoxidation method.

I. 6. Asymmetric catalytic methods based on the Weitz-Scheffer reaction

Catalysts, that are highly active and enantioselective in the epoxidation of electron rich olefins, generally give poor results in the case of electron deficient alkenes. Thus, a different strategy had to be envisaged for the epoxidation of this challenging class of olefins.

The achiral epoxidation of enones by alkaline hydrogen peroxide, known as the Weitz-Scheffer reaction, proceeds in two steps (*Scheme 45*). Initially, the Michael addition of the hydrogen-peroxide anion gives a peroxo-enolate intermediate, which then reacts further to form the epoxide ring.

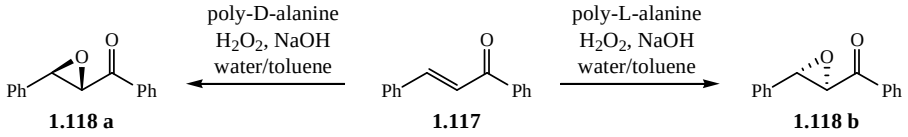


Scheme 45

The most important methods developed for the epoxidation of electron deficient alkenes are chiral, catalytic versions of the Weitz-Scheffer reaction. These catalytic systems will be presented in the following paragraphs.

I. 6. 1. Juliá-Colonna epoxidation

In 1980, Juliá reported that a synthetic polypeptide consisting solely of alanine residues was able to catalyze the epoxidation of chalcone with a high degree of enantioselectivity.[56]



Scheme 46

In a series of papers, Juliá and Colonna systematically examined and optimized the conditions for this transformation.[57] Furthermore, in subsequent years, a number of modifications and improvements have been introduced to increase the efficiency and scope of the reaction, mainly by Roberts *et al*.[58]

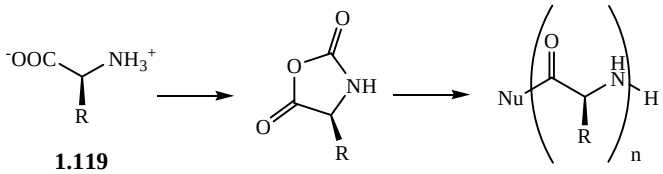
---

[56] Juliá S.; Masana J.; Vega J. C. *Angew. Chem. Int. Ed. Engl.* **1980**, *19(11)*, 929

[57] a. Juliá S.; Guixer J.; Masana J.; Rocas J.; Colonna S.; Annuziata R. ; Molinari H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1317; b. Colonna S.; Molinari H.; Banfi S.; Juliá S.; Masana J.; Alvarez A. *Tetrahedron* **1983**, *39(9)*, 1635; c. Banfi S.; Colonna S.; Molinari H.; Juliá S.; Guixer J. *Tetrahedron* **1984**, *40(24)*, 5207

[58] Reviews: a. Ebrahim S.; Wills M. *Tetrahedron: Asymmetry* **1997**, *8(19)*, 3163; b. Allen J. V.; Roberts S. M.; Williamson N. M. *Advances in Biochemical Engineering*

In addition to polyalanine (**1.121 a**), polyleucine (**1.121 b**), poly-*iso*-leucine (**1.121 c**) and poly-*neo*-pentylglycine (**1.121 d**) were found to be efficient catalysts for the asymmetric epoxidation of chalcone type substrates. Importantly, it was shown that the corresponding L- and D-poly-(amino acids) furnished the opposite enantiomers of the epoxides, as major products and in similar yields.



1.119 **1.120** **1.121**

R = Me (**a**), *i*-Bu (**b**), *s*-Bu (**c**), *neo*-Pent (**d**)

Scheme 47

The catalysts are prepared by polymerization of the corresponding *N*-carboxyanhydrides using different amine initiators (*Scheme 47*). The polymerization conditions were shown to influence the quality of the catalyst.[59] Recently, a high temperature polymerization protocol was found to be particularly beneficial.[60]

The initial condition was triphasic, consisting of the insoluble poly-(amino acid) catalyst, an aqueous solution of sodium hydroxide and hydrogen peroxide, and a solution of chalcone in toluene. Under these conditions, the reaction time is rather long, even for the most

1998, *63*, 125; c. Pu L. *Tetrahedron: Asymmetry* **1998**, *9*, 1457; d. Porter M. J.; Roberts S. M.; Skidmore J. *Bioorg. & Med. Chem.* **1999**, *7*, 2145; e. Lauret C.; Roberts S. M. *Aldrichimica Acta* **2002**, *35(2)*, 47; f. Carrea G.; Colonna S.; Kelly D. R.; Lazcano A.; Ottolina G.; Roberts S. M. *Trends in Biotechnology* **2005**, *23(10)*, 507

[59] a. Bentley P. A.; Kroutil W.; Littlechild J. A.; Roberts S. M. *Chirality* **1997**, *9*, 198; b. Baars S.; Drauz K-H.; Krimmer H-P.; Roberts S. M.; Sander J.; Skidmore J.; Zanardi G. *Organic Process Research & Development* **2003**, *7*, 509

[60] Geller T; Gerlach A.; Krüger C. M.; Militzer H-C. *Tetrahedron Lett.* **2004**, *45*, 5065

reactive substrates. Pre-conditioning of the catalyst prior to the addition of the substrate reduces somewhat the reaction time. However, the aqueous sodium hydroxide causes degradation of the polypeptide and the range of suitable substrates remains severely limited.

An important improvement of the original experimental protocol was the use of urea-hydrogen peroxide complex (UHP), together with a non-nucleophilic organic base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), in a non-aqueous system.[61] Using immobilized polyleucine under this biphasic condition, the rate of epoxidation was increased by two orders of magnitude and a larger number of substituted enones were able to react.

Moreover, phase-transfer catalysts were shown to accelerate significantly the Juliá-Colonna epoxidation under both triphasic and biphasic conditions.[62]

It has also been recognized that, inert polymer supports provide more robust catalysts. Absorption of polyleucine onto silica gel reduced the amount of catalyst needed by 75% and made the recovery of the reaction product and recycling of the catalyst easier.[63]

[61] Bentley P. A. Bergeron S.; Cappi M. W.; Hibbs D. E.; Hursthouse M. B.; Nugent T. C.; Pulido R.; Roberts S. M.; Wu L. E. *Chem. Commun.* **1997**, 739
[62] a. Geller T.; Gerlach A.; Krüger C. M.; Militzer H-C. *Tetrahedron Lett.* **2004**, *45*, 5065; b. Geller T.; Krüger C. M.; Militzer H-C. *Tetrahedron Lett.* **2004**, *45*, 5069
[63] a. Geller T.; Roberts S. M. *J. Chem. Soc., Perkin Trans. 1*. **1999**, 1397; b. Dhanda A.; Drauz K-H.; Geller T.; Roberts S. M. *Chirality* **2000**, *12*, 313

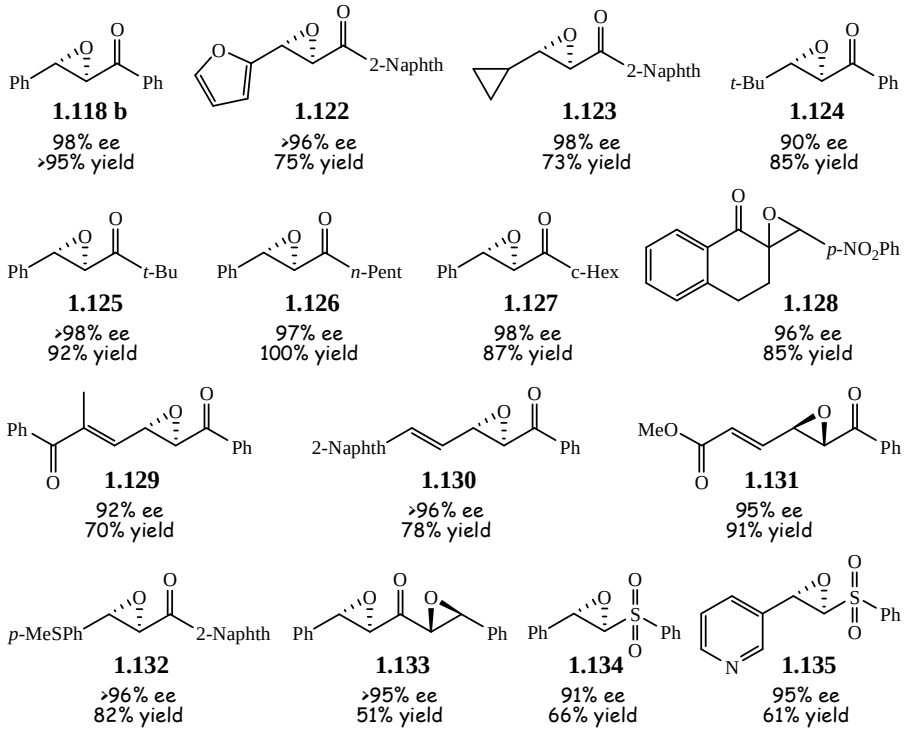
The most common oxidant remains hydrogen peroxide, but other oxidants, such as sodium perborate and sodium percarbonate have also been used successfully.[64]

The original triphasic condition gave excellent results only in the case of chalcone and its simple analogues. However, the improved systems enable the efficient asymmetric epoxidation of a broader range of enones.[65] Electron donating and electron withdrawing substituents on the phenyl groups are well tolerated. Both phenyl groups of the chalcone can be replaced by other aromatic substituents, such as naphthyl, pyridyl or furyl. The aryl substituent next to the carbonyl function can be replaced by different alkyl groups whilst preserving the high yield and enantioselectivity of the process. However, only *t*-butyl and cyclopropyl substituents give excellent results when replacing the aromatic ring next to the alkene function. A further limitation is that, apart from special cases, the trisubstituted alkenones do not react under these conditions. On the other hand, the

[64] a. Lasterra-Sánchez M. E.; Roberts S. M. *J. Chem. Soc., Perkin Trans.* 1 **1995**, 1467 ; b. Savizky R. M.; Suzuki N.; Bové J. L. *Tetrahedron: Asymmetry* **1998**, *9*, 3967; c. Allen J. V.; Drauz K-H.; Flood R. W.; Roberts S. M.; Skidmore J. *Tetrahedron Lett.* **1999**, *40*, 5417

[65] Substrate scope: a. Lasterra-Sánchez M. E.; Felfer U.; Mayon P.; Roberts S. M.; Thornton S. R.; Todd C. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 343; b. Lasterra-Sánchez M. E.; Roberts S. M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1467; c. Kroutil W.; Lasterra-Sánchez M. E.; Maddrell S. J.; Mayon P.; Morgan P.; Roberts S. M.; Thornton S. R.; Todd C. J.; Tüter M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2837; d. Kroutil W.; Mayon P.; Lasterra-Sánchez M. E.; Maddrell S. J.; Roberts S. M.; Thornton S. R.; Todd C. J.; Tüter M. *Chem. Commun.* **1996**, 845; e. Allen J. V.; Cappi M. W.; Kary P. D.; Roberts S. M.; Williamson N. M.; Wu L. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3297; f. Allen J. V.; Bergeron S.; Griffiths M. J.; Mukherjee S.; Roberts S. M.; Willianson N. M.; Wu L. E. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3171; g. Ray P. C.; Roberts S. M. *Tetrahedron Lett.* **1999**, *40*, 1779; h. Bentley P. A.; Bickley J. F.; Roberts S. M.; Steiner A. *Tetrahedron Lett.* **2001**, *42*, 3741; i. Lopez-Pedrosa J-M.; Pitts M. R.; Roberts S. M.; Saminathan S.; Whittall J. *Tetrahedron Lett.* **2004**, *45*, 5073

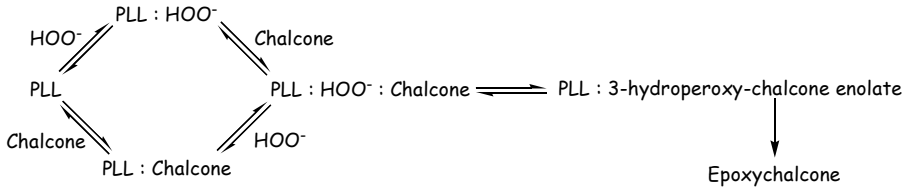
selectivity of this method for the epoxidation of electron poor double bonds allows the regioselective epoxidation of variously substituted polyenes. Moreover, under the fine-tuned conditions, sulphur containing enones can be chemoselectively epoxidized. Electron-deficient alkenes other than *α,β*-unsaturated ketones are generally unreactive, with the exception of some *α,β*-unsaturated esters and sulfones. Furthermore, it is noteworthy that, despite all these several improvements, the substrate scope remains restricted to *trans* enones. Some of the best results are represented in *Scheme 48*.



Scheme 48

Several efforts have been made to elucidate the mechanism of the Juliá-Colonna epoxidation in order to further expand the scope of this reaction. Recently, the synthesis of soluble, polyethylene-glycol bound poly-L-leucine allowed the examination of kinetic

parameters.[66] Based on these studies, poly-L-leucine behaves as an enzyme-like catalyst at relatively low concentrations of substrates, and shows saturation kinetics for both chalcone and hydrogen peroxide anion. A so called steady-state random bireactant mechanism was proposed (*Scheme 49*). Two pathways have been proposed to lead to a ternary complex containing polyleucine, chalcone and hydrogen peroxide anion. One of the pathways, in which the hydrogen peroxide anion binds initially to the polymer, appears to be kinetically favoured over the other. All the substrates must bind to the catalyst to form this key complex before the generation of the hydroperoxide enolate of chalcone, which eventually forms epoxychalcone.



Scheme 49

The catalytic properties of various oligopeptides have been investigated to understand the exact origin of the asymmetric induction. From these studies, it has been speculated that increased α-helical character of the poly-(amino acid) secondary structure enhances the catalytic activity and leads to a high degree of asymmetric induction, while increased β-sheet character is detrimental.[67] However, the excellent catalytic efficiency of poly-L-

[66] a. Carrea G.; Colonna S.; Meek A. D.; Ottolina G.; Roberts S. M. *Chem. Commun.* **2004**, 1412; b. Carrea G.; Colonna S.; Meek A. D.; Ottolina G.; Roberts S. M. *Tetrahedron: Asymmetry* **2004**, *15*, 2945

[67] a. Colonna S.; Molinari H.; Banfi S.; Juliá S.; Masana J.; Alvarez A. *Tetrahedron* **1983**, *39(9)*, 1635; b. Kelly D. R.; Bui T. T.; Caroff E.; Drake A. F.; Roberts S. M. *Tetrahedron Lett.* **2004**, *45*, 3885

iso-leucine, which possesses an important *β*-sheet secondary structure, is not consistent with this proposal.

Both yields and enantiomeric excesses were found to be dependent on the molecular weight of the polypeptide. The synthesis of the poly-(amino acid) chains stepwise, using automated peptide synthesizer, enabled careful structure-efficiency relationship studies to be established.[68] It has been demonstrated that, the chiral matrix adjacent to the amino terminus determines the stereochemistry of the product. Although the parts of the polymer farther away from the amino end have very little effect on enantioselectivity, they are important as well, probably for building up the correct chiral architecture.

The role of hydrogen bonding in setting up the chiral environment was demonstrated by the formation of racemic epoxide when using methanol as solvent.[69] The four amino terminal N-H groups of an *α*-helical polypeptide do not participate in intrachain hydrogen bonds. Hence, they are ideally available for binding the enones and peroxyenolates. Model studies concluded that the origin of the enantioselective catalysis is probably a combination of the hydrogen bonding motif and the helical conformation, which envelops the substrate so as to shelter one face of the double bond.[70]

[68] a. Bentley P. A.; Cappi M. W.; Flood R. W.; Roberts S. M.; Smith J. A. *Tetrahedron Lett.* **1998**, *39*, 9297; b. Bentley P. A.; Flood R. W.; Roberts S. M.; Skidmore J.; Smith C. B.; Smith J. A. *Chem. Commun.* **2001**, 1616; c. Flood R. W.; Geller T. P.; Petty S. A.; Roberts S. M.; Skidmore J.; Volk M. *Org. Lett.* **2001**, *3(5)*, 683; d. Berkessel A.; Gasch N.; Glaubitz K.; Koch C. *Org. Lett.* **2001**, *3(24)*, 3839

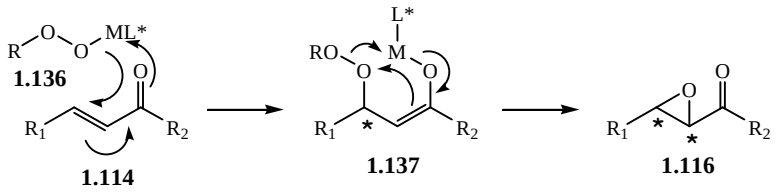
[69] Colonna S.; Molinari H.; Banfi S.; Juliá S.; Masana J.; Alvarez A. *Tetrahedron* **1983**, *39(9)*, 1635

[70] Kelly D. R.; Roberts S. M. *Chem. Commun.* **2004**, 2018

As a result of the numerous studies and developments, the Juliá-Colonna epoxidation became a particularly efficient method even for industrial scale synthesis. However, its relatively narrow substrate scope calls for further research in the field of the asymmetric epoxidation of electron-deficient double bonds.

I. 6. 2. Lanthanide-BINOL complexes

Several methods for the asymmetric epoxidation of electron-deficient alkenes rely on the use of a chiral ligand coordinated to a metal peroxide, which then executes a Weitz-Scheffer reaction (*Scheme 50*).

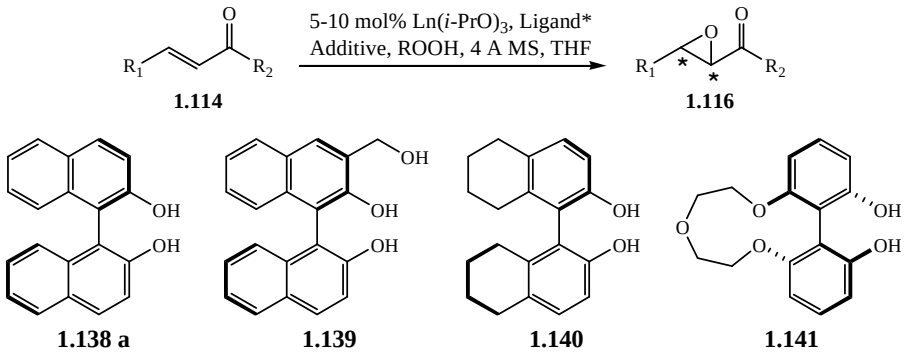


Scheme 50

A number of metals, such as lithium, magnesium, zinc and various lanthanides were tested, with the combination of optically active ligands.[71] Among these methods, the best results were obtained by Shibazaki and co-workers using lanthanide-BINOL complexes (*Scheme 51*). They reported their first, very promising results on the

[71] Li: Tanaka Y.; Nishimura K.; Tomioka K. *Tetrahedron* **2003**, *59*, 4549; Mg: a. Elston C. L.; Jackson R. F. W.; MacDonald S. J. F.; Murray P. J. *Angew. Chem. Int. Ed. Engl.* **1997**, *36(4)*, 411; b. Jacques O.; Richards S. J.; Jackson R. F. W. *Chem. Commun.* **2001**, 2712; Zn: a. Enders D.; Zhu J.; Raabe G. *Angew. Chem. Int. Ed. Engl.* **1996**, *35(15)*, 1725; b. Enders D.; Kramps L.; Zhu J. *Tetrahedron: Asymmetry* **1998**, *9*, 3959; c. Yu H.-B.; Zheng X.-F.; Lin Z.-M.; Hu Q.-S.; Huang W.-S.; Pu L. *J. Org. Chem.* **1999**, *64*, 8149

asymmetric epoxidation of enones in 1997. Since then, they fine-tuned the conditions for differently substituted enones, amides and esters.[72]



Scheme 51

The most commonly used catalyst is generated from La(*i*-PrO)$_3$, BINOL and $Ph_3As{=}O$ in a ratio of 1:1:1. However, in certain cases, a combination of other metals, such as Yb, Pr, Sm or Y, with ligands **1.139**, **1.140**, **1.141** gives the best results. The presence of molecular sieves seems to be crucial. Interestingly, even in cases where addition of water increases the efficiency of the catalyst, the presence of molecular sieves remains essential.[73]

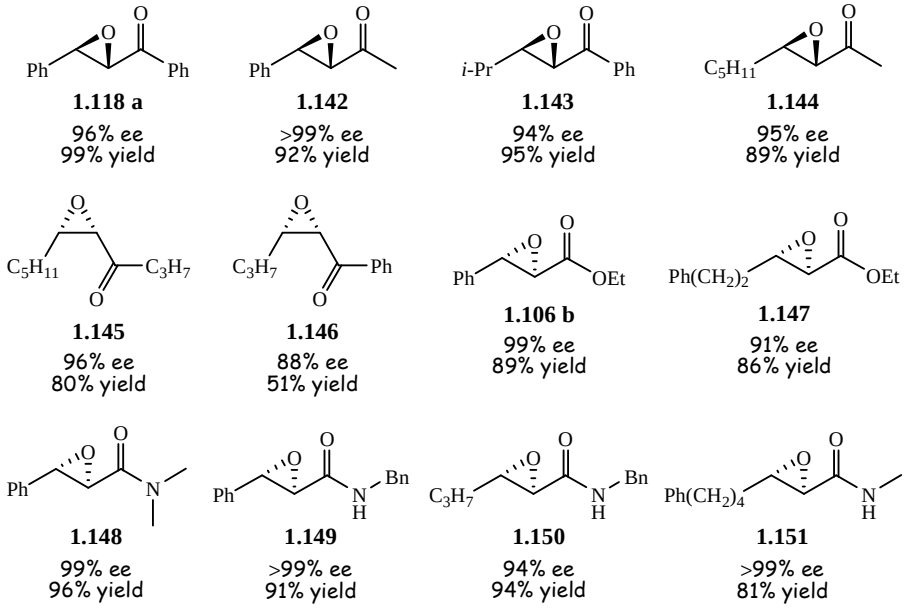
This method proved to be particularly efficient for a wide range of *trans* aromatic and aliphatic enones, *β*-alkyl and *β*-aryl substituted amides and esters.[74] Among *cis* alkenes, aliphatic enones

[72] Bougauchi M.; Watanabe S.; Arai T.; Sasai H.; Shibasaki M. *J. Am. Chem. Soc.* **1997**, *119*, 2329

[73] Watanabe S.; Kobayashi Y.; Arai T.; Sasai H.; Bougauchi M.; Shibasaki M. *Tetrahedron Lett.* **1998**, *39*, 7353

[74] a. Nemoto T.; Ohshima T.; Yamaguchi K.; Shibasaki M. *J. Am. Chem. Soc.* **2001**, *123*, 2725; b. Chen R.; Qian C.; Vries J. G. *Tetrahedron Lett.* **2001**, *42*, 6919; c. Chen R.; Qian C.; Vries J. G. *Tetrahedron* **2001**, *57*, 9837; d. Kumaraswamy G.; Sastry M. N. V.; Jena N.; Kumar K. R.; Vairamani M. *Tetrahedron: Asymmetry* **2003**, 14, 3797; e. Ohshima T.; Nemoto T.; Tosaki S.; Kakei H.; Gnanadesikan V.; Shibasaki M. *Tetrahedron* **2003**, *59*, 10485; f. Kinoshita T.; Okada S.; Park S.-R.;

can be epoxidized with high enantioselectivities, while the aromatic derivatives tend to isomerize.[75] A few, representative examples of the best results can be seen in *Scheme 52*.



Scheme 52

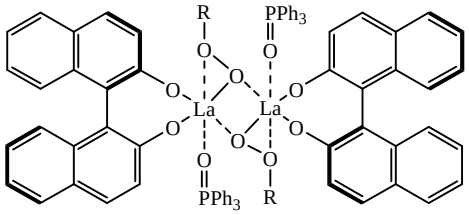
Great efforts have been made to elucidate the exact structure of the active complex and that of the transition state. It was shown that additives, such as triphenylphosphine oxide or triphenylarsine oxide, increase the yield and the enantioselectivity of the reaction.[76] It is believed that these additives, coordinating to the metal centre, break the oligomer structure of the catalyst.

Matsunaga S.; Shibasaki M. *Angew. Chem. Int. Ed.* **2003**, *42*, 4680; g. Kakei H.; Tsuji R.; Ohshima T.; Shibasaki M. *J. Am. Chem. Soc.* **2005**, *127*, 8962

[75] Watanabe S.; Arai T.; Sasai H.; Bougauchi M. ; Shibasaki M. *J. Org. Chem.* **1998**, *63*, 8090

[76] a. Daikai K.; Kamaura M.; Inanaga J. *Tetrahedron Lett.* **1998**, *39*, 7321; b. Nemoto T.; Ohshima T.; Yamaguchi K.; Shibasaki M. *J. Am. Chem. Soc.* **2001**, *123*, 2725

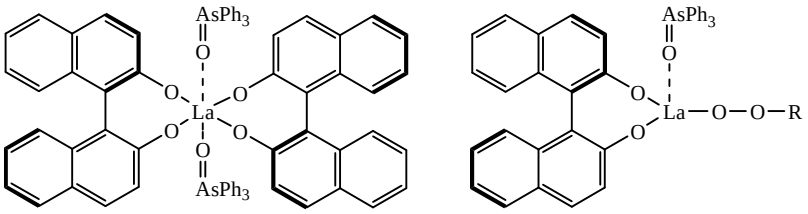
Inanaga proposed a homochiral dimeric μ-complex as the active species (*Scheme 53*). He suggested that one of the lanthanide ions may work as a Lewis acid, to activate and control the orientation of the enone, while the peroxide attached to the other lanthanide ion performs the oxidation.[77]



1.152

Scheme 53

Meanwhile, Shibazaki proposed the existence of the precatalyst **1.153** and of the monomeric species **1.154**, as the most active catalytic species (*Scheme 54*).[78] He believes that the same metal activates the enone and delivers the peroxide, hence performing the oxidation. However, the participation of several complexes cannot be completely excluded.



1.153 **1.154**

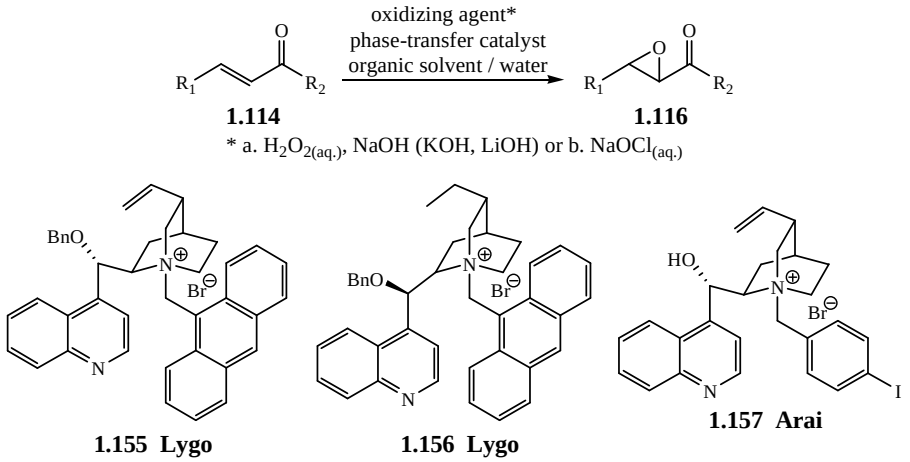
Scheme 54

[77] a. Inanaga J.; Furuno H.; Hayano T. *Catalysis Surveys from Japan* **2001**, *5(1)*, 37; b. Daikai K.; Hayano T.; Kino R.; Furuno H.; Kagawa T.; Inanaga J. *Chirality* **2003**, *15*, 83

[78] Nemoto T.; Ohshima T.; Yamaguchi K.; Shibasaki M. *J. Am. Chem. Soc.* **2001**, *123*, 2725

I. 6. 3. Phase-transfer catalysis

Promising results have been obtained in the asymmetric epoxidation of electron-deficient alkenes by phase-transfer catalysis. Wynberg showed the first example of such reaction using alkaloid derived quaternary ammonium salts as catalyst.[79] The initial, moderate enantioselectivities were increased by the group of Arai and Lygo.[80] Their best catalysts are represented below.



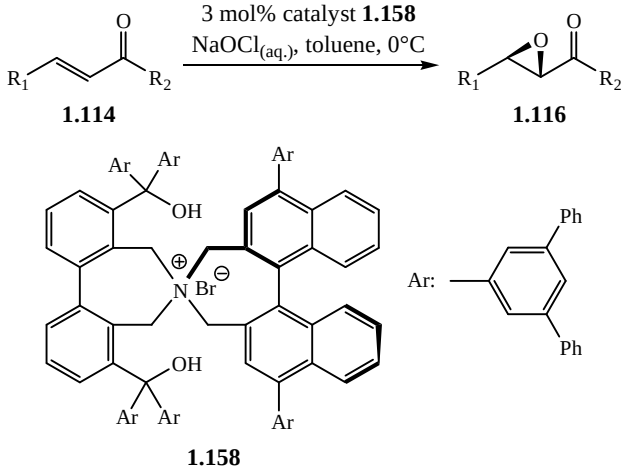
Scheme 55

Maruoka obtained even better results using a new class of quaternary ammonium catalysts (*Scheme 56*).[81]

[79] a. Helder R.; Hummelen J. C.; Laane R. W. P. M.; Wiering J. S.; Wynberg H. *Tetrahedron Lett.* **1976**, *21*, 1831; b. Wynberg H.; Greijdanus B. *Chem. Commun.* **1978**, 427

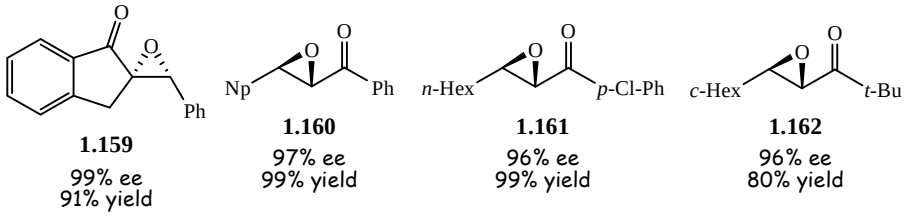
[80] a. Lygo B.; Wainwright P. G. *Tetrahedron Lett.* **1998**, *39*, 1599; b. Lygo B.; Wainwright P. G. *Tetrahedron* **1999**, *55*, 6289; c. Lygo B.; To D. C. M. *Tetrahedron Lett.* **2001**, *42*, 1343; d. Arai S.; Tsuge H.; Shioiri T. *Tetrahedron Lett.* **1998**, *39*, 7563; e. Arai S.; Tsuge H.; Oku M.; Miura M.; Shioiri T. *Tetrahedron* **2002**, *58*, 1623

[81] Ooi T.; Ohara D.; Tamura M. ; Maruoka K. *J. Am. Chem. Soc.* **2004**, *126(22)*, 6844



Scheme 56

Using this latter catalytic system, up to *99%* enantioselectivity was reached, not only for differently substituted chalcone derivatives, but also for certain alkyl substituted enones. Representative examples can be seen below.

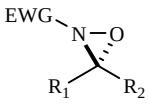


Scheme 57

I. 7. Other promising asymmetric oxidizing systems

In addition to the above mentioned, highly successful catalysts numerous other metal-ligand combinations have been tested for catalytic asymmetric epoxidation. Moreover, several efforts have been made in the field of organocatalysis, inspired by the success of chiral ketone catalysts.

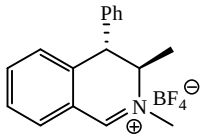
Analogously to dioxiranes, oxaziridines can be generated from imines upon oxidation. However, oxaziridines need to be activated to perform epoxidation (*Scheme 58*). Davis demonstrated that chiral *N*-sulfonyl oxaziridines are able to induce asymmetry in alkene epoxidation.[82] Unfortunately, due to the moderate yields and enantioselectivities obtained so far, a catalytic version of this oxidation protocol has not yet been developed.



1.163

Scheme 58

In contrast to oxaziridines, *in situ* generated chiral oxaziridinium salts were shown to be efficient epoxidation catalysts. In 1993, Bohé prepared the chiral iminium salt **1.164** and applied it to the catalytic asymmetric epoxidation of simple alkenes.[83] Since then, several chiral iminium salts have been tested by different research groups.[84]



1.164

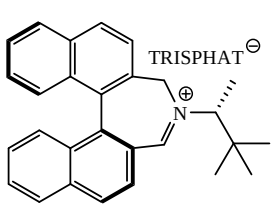
Scheme 59

[82] a. Davis F. A.; Harakal M. E.; Awad S. B. *J. Am. Chem. Soc.* **1983**, *105(10)*, 3123; b. Davis F. A.; Reddy R. T.; McCauley J. P.; Przeslawski R. M.; Harakal M. E.; Carroll P. J. *J. Org. Chem.* **1991**, *56(2)*, 809

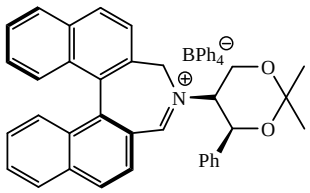
[83] Bohé L.; Hanquet G.; Lusinchi M.; Lusinchi X. *Tetrahedron Lett.* **1993**, *34(45)*, 7271

[84] Wong O. A.; Shi Y. *Chem. Rev.* **2008**, *108*, 3958 and references therein

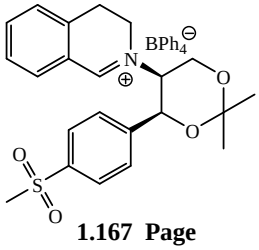
A systematic study of several structural parameters led to the most enantioselective iminium catalysts available today. These are displayed in *Scheme 60*. Lacour showed that the use of TRISPHAT (tris[tetrachlorobenzene-diolato]phosphate (V)) counter-ion is beneficial for the yield and enantioselectivity, since it increases the solubility of the catalyst in the organic phase.[85] An important improvement was the development of non-aqueous conditions by using TPPP (tetraphenylphosphonium monoperoxysulfate) instead of oxone. [86]



1.165 Lacour



1.166 Page

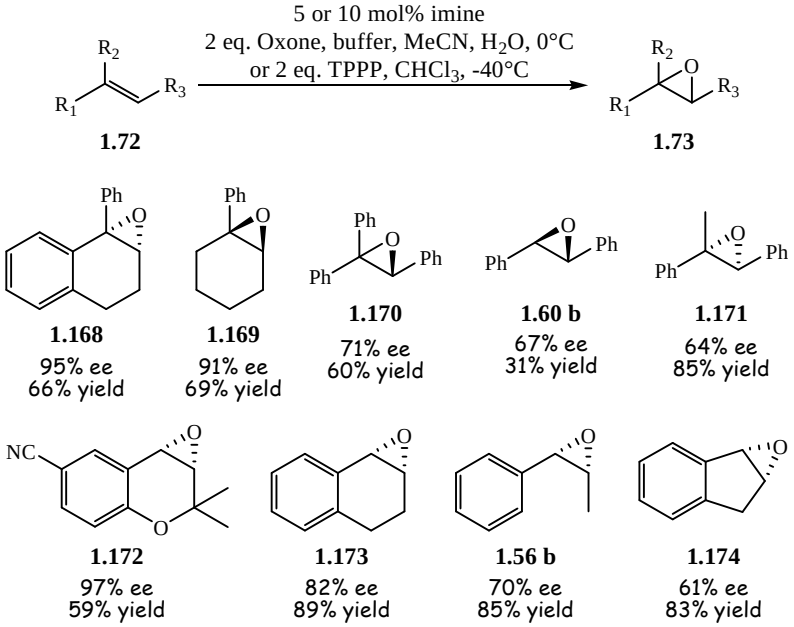


1.167 Page

Scheme 60

Generally, conjugated trisubstituted olefins are the best substrates for oxaziridinium-mediated epoxidation in term of enantioselectivity, while *cis* olefins are poor substrates. However, catalyst **1.167**, prepared by Page, gives high asymmetric induction under non-aqueous conditions for some conjugated *cis* olefins.[87] The best results obtained by iminium-catalyzed asymmetric epoxidation are presented below.

[85] Vachon J.; Pérollier C.; Monchaud D.; Marsol C.; Ditrich K.; Lacour J. *J. Org. Chem.* **2005**, *70*, 5903
[86] Page P. C. B.; Barros D.; Buckley B. R.; Ardakani A.; Marples B. A. *J. Org. Chem.* **2004**, *69*, 3595
[87] a. Page P. C. B.; Buckley B. R.; Heaney H.; Blacker A. J. *Org. Lett.* **2005**, *7(3)*, 375; b. Page P. C. B.; Buckley B. R.; Barros D.; Blacker A. J.; Heaney H.; Marples B. A. *Tetrahedron* **2006**, *62*, 6607



Scheme 61

As can be seen, the enantiomeric excesses are encouraging but, apart from one or two substrates, this method has not yet reached synthetically useful levels of enantioselectivities.

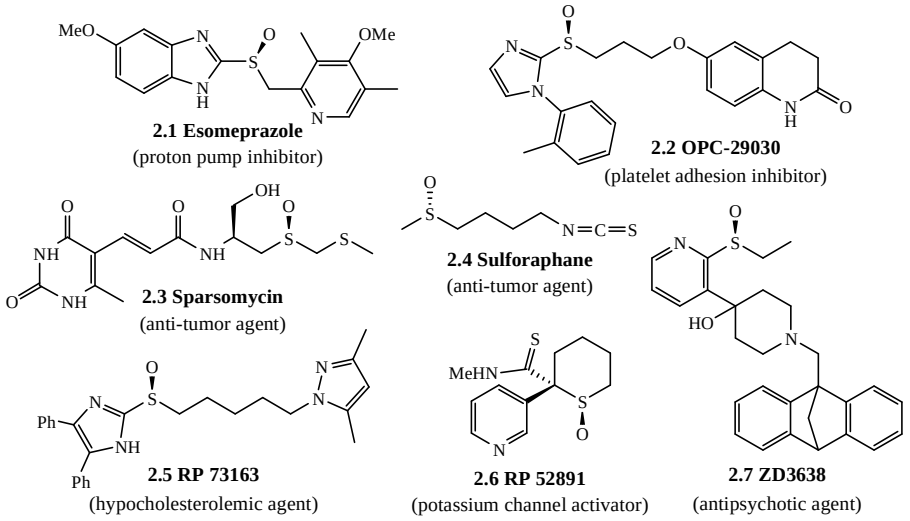
Interestingly, the corresponding amines have been recently shown to give similar results to the imines.[88] The mechanism of this latter system is still under investigation.

[88] a. Armstrong A. *Angew. Chem. Int. Ed. Engl.* **2004**, *43*, 1460; b. Gonçalves M-H.; Martinez A.; Grass S.; Page P. C. B.; Lacour J. *Tetrahedron Lett.* **2006**, *47*, 5297; c. Vachon J.; Lauper C.; Ditrich K.; Lacour J. *Tetrahedron: Asymmetry* **2006**, *17*, 2334

II. Catalytic asymmetric sulfoxidation of prochiral sulfides

II. 1. Introduction

Optically active sulfoxides are not only key intermediates in the synthesis of numerous biologically active compounds, but some of them possess important pharmacological properties.[89] Several sulfinyl-substituted benzimidazoles are applied as proton pump inhibitors in the treatment of gastric ulcer. In addition, natural products such as sparsomycin **2.3** and sulforaphane **2.4** are intensively investigated for their anti-tumor activity.



Scheme 62

In a number of cases, the stereochemistry of the sulfinyl group proved to influence the biological activity of the given molecule. The proton pump inhibitor esomeprazol **2.1** or the platelet adhesion inhibitor OPC-29030 **2.2** showed better pharmacological profile than

[89] Legros J.; Dehli J. R.; Bolm C. *Adv. Synth. Catal.* **2005**, *347*

the corresponding opposite enantiomers or the racemic mixtures. In certain cases, the enantiomer pair of the biologically active sulfoxide is completely inactive. Representative examples are the hypocholesterolemic agent RP 73163 **2.5** or the potassium channel activator RP 52891 **2.6**. More importantly, it has been observed in some cases, that the opposite enantiomer had detrimental effect on the organism and only the enantiopure compound can be administered. For example, the antipsychotic agent ZD3638 **2.7**, tested for the treatment of schizophrenia, was required to have an enantiomeric excess greater than *99%*.

As mentioned above, chiral sulfoxides are frequently used as key intermediates in the synthesis of biologically active molecules. The high efficiency of sulfoxides as chiral auxiliaries is the result of the steric differences between the lone pair of electrons, the oxygen and the two different carbon substituents of the stereogenic sulphur atom. The oxygen atom of the sulfoxide can coordinate to a metal ion or a proton, increasing further its stereodirecting ability. Interestingly, the chiral sulfoxide is able to differentiate the diastereotopic faces of a proximal and even a remote reaction centre. Additionally, the electron-withdrawing sulfinyl group can activate a neighbouring double bond for conjugate addition and stabilizes the corresponding α-carbanion.

Reduction of *β*-keto sulfoxides, Michael addition of nucleophiles to *α,β*-unsaturated sulfoxides, carbon-carbon bond formation using sulfoxide-stabilized carbanions, Diels-Alder reactions of vinyl sulfoxides and Pummerer reactions are the most common diastereoselective transformations using sulfoxide as chiral auxiliaries.

Furthermore, optically active sulfoxides are used as chiral ligands in metal-catalyzed enantioselective reactions, for example, in rhodium or iridium catalyzed hydrogenation reactions, iron, copper or magnesium catalyzed cycloadditions and palladium catalyzed allylic substitutions.[90]

In the total synthesis of biologically active molecules, the formation of chiral sulfoxides by Andersen's procedure is still regularly employed.[91] This method is based on the stereospecific nucleophilic substitution reaction of a chiral sulfinate with an organometallic reagent. However, the formation of enantiopure sulfoxides requires several steps including the synthesis of the chiral sulfinyl transfer agent.[92] Thus, an efficient catalytic system for the direct asymmetric oxidation of prochiral sulfides would be a much more elegant and atom economic method. The most important improvements in this field will be presented in this chapter.

II. 2. Modified Sharpless method

Inspired by the success of the Sharpless-Katsuki reagent in the asymmetric epoxidation of allylic alcohols, Kagan and Modena independently studied the applicability of this method for asymmetric sulfoxidation reactions. The original condition had to be modified by the addition of water and/or increased amount of diethyl tartrate to obtain high asymmetric induction in the oxidation of prochiral

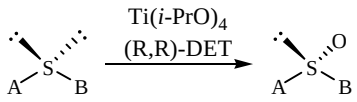
[90] Reviews: a. Carreño M. C. *Chem. Rev.* **1995**, *95*, 1717; b. Matsuyama H. *Sulfur Reports* **1999**, *22*, 85; c. Fernández I.; Khiar N. *Chem. Rev.* **2003**, *103*, 3651; d. Pellissier H. *Tetrahedron* **2006**, *62*, 5559

[91] Andersen K. K. *Tetrahedron Lett.* **1962**, *3*, 93

[92] Variety of chiral sulfinyl transfer agents: Han Z.; Krishnamurthy D.; Grover P.; Fang Q. K.; Su X.; Wilkinson H. S.; Lu Z.-H.; Magiera D.; Senanayake C. H. *Tetrahedron* **2005**, *61*, 6386 and references therein

sulfides. Kagan published the ratio of Ti(*i*-PrO)$_4$: DET : H_2O = 1:2:1 as the ideal combination, while Modena obtained similar results using Ti(*i*-PrO)$_4$: DET = 1:4 without the addition of water.[93]

The following model was presented to predict the stereochemical outcome of the reaction (*Scheme 63*). The **A** group represents a large aromatic or benzyl group and **B** a small alkyl substituent.



2.8 **2.9**

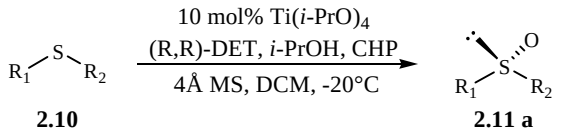
Scheme 63

Further modification of the Kagan system, such as using cumyl hydroperoxide instead of *t*-butyl hydroperoxide as the stoichiometric oxidant and adding molecular sieves to the reaction before the formation of the catalyst, led to a decrease in the amount of Ti(*i*-PrO)$_4$ to 20 mol% without significant lowering of the enantioselectivity.[94] Later on, the Ti(*i*-PrO)$_4$: DET : *i*-PrOH = 1:4:4 condition was published to allow the use of only 10 mol% catalyst in the presence of molecular sieves.[95] These conditions, in which water is replaced by isopropanol, can be considered as a combination of Kagan's and Modena's systems.

[93] a. Pitchen P.; Kagan H. B. *Tetrahedron Lett.* **1984**, *25(10)*, 1049 ; b. Furia F. D.; Modena G.; Seraglia R. *Synthesis* **1984**, 325; c. Pitchen P.; Duñach E.; Deshmukh M. N.; Kagan H. B. *J. Am. Chem. Soc.* **1984**, *106(26)*, 8188; d. Zhao S. H.; Samuel O.; Kagan H. B. *Tetrahedron* **1987**, *43(21)*, 5135; e. Brunel J-M.; Diter P.; Duetsch M.; Kagan H. B. *J. Org. Chem.* **1995**, *60*, 8086

[94] a. Zhao S. H.; Samuel O.; Kagan H. B. *Tetrahedron* **1987**, *43(21)*, 5135; b. Kagan H. B.; Rebiere F. *Synlett* **1990**, 643

[95] a. Brunel J-M.; Kagan H. B. *Bull. Soc. Chim. Fr.* **1996**, *133*, 1109; b. Brunel J-M.; Kagan H. B. *Synlett* **1996**, 404

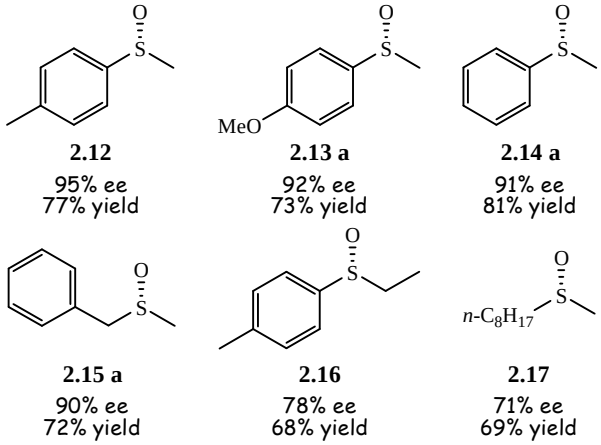


2.10 **2.11 a**

up to *95%* ee

Scheme 64

The scope and limitations of these new catalytic conditions have been studied. Using this method, high enantioselectivities can be obtained for different aryl methyl sulfides. When the aromatic substituent is replaced by a benzyl group, the asymmetric induction remains high. In contrast, alkyl substituents in place of the aryl group, as well as, any aromatic or aliphatic substituent replacing the methyl group, lead to a significant decrease in the enantioselectivity. Representative examples of the best results are shown in *Scheme 65*.



2.12 95% ee 77% yield

2.13 a 92% ee 73% yield

2.14 a 91% ee 81% yield

2.15 a 90% ee 72% yield

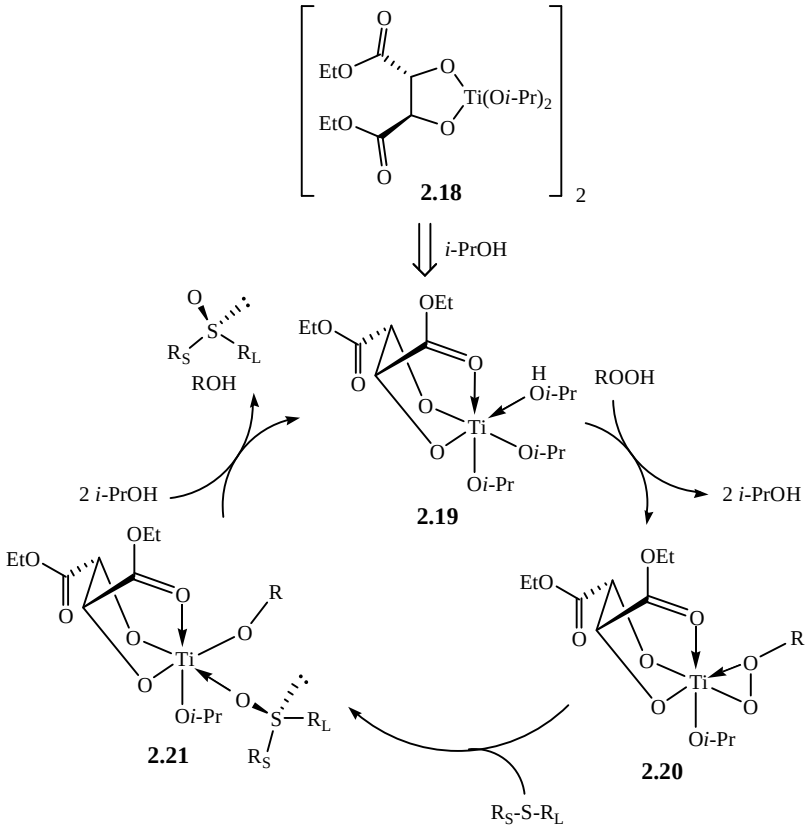
2.16 78% ee 68% yield

2.17 71% ee 69% yield

Scheme 65

Although the exact structure of the active catalytic species is not well established, a catalytic cycle has been proposed (*Scheme 66*). It is suggested that, in the presence of isopropanol, the equilibrium between the different catalytic species is shifted towards the formation of a monomeric complex **2.19**. Futhermore, the isopropanol is

probably beneficial in the regeneration of the active catalytic species, replacing the formed sulfoxide in the coordination sphere of the titanium.

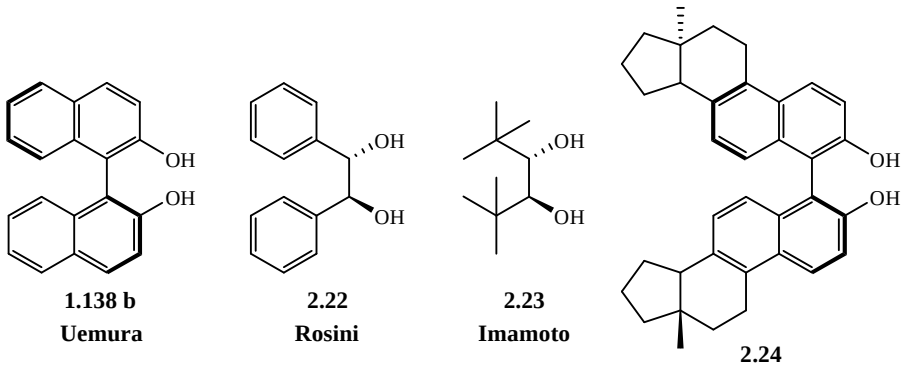


Scheme 66

Several attempts have been made to replace the diethyltartrate ligand by different chiral diols. The highest enantioselectivities were achieved using ligands depicted in *Scheme 67*.[96] Modification of these

[96] a. Komatsu N.; Nishibayashi Y.; Sugita T.; Uemura S. *Tetrahedron Lett.* **1992**, *33(37)*, 5391; b. Komatsu N.; Hashizume M.; Sugita T.; Uemura S. *J. Org. Chem.* **1993**, *58*, 4529; c. Yamanoi Y.; Imamoto T. *J. Org. Chem.* **1997**, *62*, 8560; d. Superchi S.; Rosini C. *Tetrahedron: Asymmetry* **1997**, *8(3)*, 349; e. Superchi S.; Donnoli M. I.; Rosini C. *Tetrahedron Lett.* **1998**, *39*, 8541; f. Donnoli M. I.; Superchi S.; Rosini C. *J. Org. Chem.* **1998**, 6*3*, 9392; g. Bolm C.; Dabard O. A. G.; *Synlett* **1999**, *3*, 360

ligands by different substituents and partial saturation of the binol ligand gave inferior results, changing even the sense of asymmetric induction in certain cases.[97] We have to point out, that usually, under conditions allowing over *90%* enantioselectivity, kinetic resolution plays a significant role, which decreases the yield of the sulfoxide. The steroid-derived ligand **2.24** of Bolm is a remarkable exception. Up to *92%* enantioselectivity can be achieved using this ligand without sulfone formation. It is noteworthy, that the binol part of the ligand determines the absolute stereochemistry of the major product and that the right steroid configuration has a matched effect.



1.138 b **Uemura** | **2.22** **Rosini** | **2.23** **Imamoto** | **2.24** **Bolm**

Scheme 67

Similarly to the original Kagan-Modena complex, aryl methyl sulfides are the ideal substrates for these new catalysts, whilst other aryl alkyl or dialkyl sulfides are oxidized with far lower enantioselectivities.

[97] a. Yamamoto K.; Ando H.; Shuetake T.; Chikamatsu H. *J. Chem. Soc., Chem. Commun.* **1989**, 754; b. Reetz M. T.; Merk C.; Naberfeld G.; Rudolph J.; Griebenow N.; Goddard R. *Tetrahedron Lett.* **1997**, *38(30)*, 5273; c. Martyn L. J. P.; Pandaraju S.; Yudin A. K. *J. Organomet. Chem.* **2000**, *603*, 98

II. 3. Biological systems

Besides the direct catalytic asymmetric sulfoxidation of prochiral sulfides by chemical reagents, promising results have been obtained using biological systems. Both whole cell microorganisms and isolated enzymes have been successfully applied to the asymmetric sulfoxidation of certain substrates.[98] The use of whole cells, avoiding the need of enzyme isolation and cofactor regeneration, would be an ideal biochemical method. However, better results have been obtained with isolated enzymes. An important drawback of these biochemical methods is the high substrate structure dependence of the obtained enantioselectivity. Cyclohexanone mono-oxygenase has been shown to be the most effective and general enzyme for the enantioselective synthesis of sulfoxides.[99] However, excellent enantioselectivities have been obtained only when the sulfide had one aromatic or bulky aliphatic substituent on one side and a small, ideally methyl group, on the other side. Additionally, remarkable results have been obtained by different haloperoxidases.[100]

II. 4. Porphyrin systems

Similarly to asymmetric epoxidation, several porphyrin complexes, which mimic the active site of enzymes, have been tested

[98] a. Holland H. L. *Chem. Rev.* **1988**, *88*, 473; b. Holland H. L.; Brown F. M.; Larsen B. G. *Tetrahedron: Asymmetry* **1995**, *6(7)*, 1561; c. Holland H. L.; Brown F. M.; Lakshmaiah G.; Larsen B. G.; Patel M. *Tetrahedron: Asymmetry* **1997**, *8(5)*, 683; d. Colonna S.; Del Sordo S.; Gaggero N.; Carrea G.; Pasta P. *Heteroatom Chemistry* **2002**, *13(5)*, 467

[99] a. Colonna S.; Gaggero N.; Manfredi A.; Casella L.; Gullotti M. *J. Chem. Soc., Chem. Commun.* **1988**, 1451; b. Colonna S.; Gaggero N.; Bertinotti A.; Carrea G.; Pasta P. *J. Chem. Soc., Chem. Commun.* **1995**, 1123; c. Colonna S.; Gaggero N.; Carrea G.; Pasta P. *J. Chem. Soc., Chem. Commun.* **1997**, 439; d. Colonna S.; Del Sordo S.; Gaggero N.; Carrea G.; Pasta P. *Heteroatom Chemistry* **2002**, *13(5)*, 467

[100] Dembitsky V.M. *Tetrahedron* **2003**, *59*, 4701

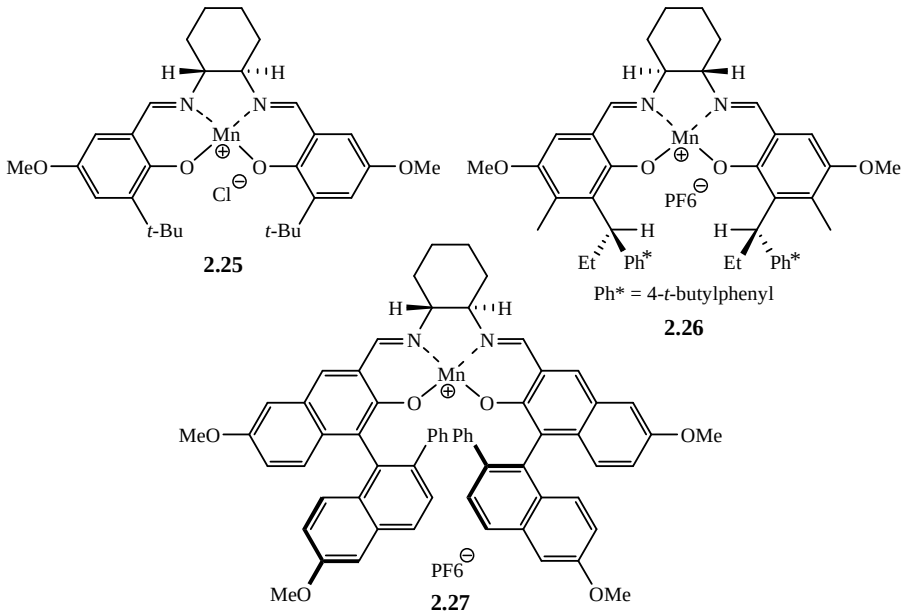
in sulfoxidation reactions. However, to the best of our knowledge, the highest enantioselectivity obtained with the various iron and manganese porphyrins does not exceed *75%*.[101]

II. 5. Schiff base complexes

Jacobsen and Katsuki applied also their system, developed for the asymmetric epoxidation of simple olefins, to the asymmetric oxidation of prochiral sulfides.[102] Both of them had to adjust the structure of their best epoxidation catalysts to optimize the level of asymmetric induction. Katsuki pointed out that, in their complexes, not only the ideal substitution patterns were different, but the matched and mismatched pairs of the chiral elements were opposite for epoxidation and sulfoxidation reactions. To rationalize these observations, he proposed that sulfides follow the same pathway to coordinate to the metal centre as the alkenes, but their substituents are differently positioned due to the sp^3 configuration. The most efficient Jacobsen's and Katsuki's catalysts are presented in *Scheme 68*.

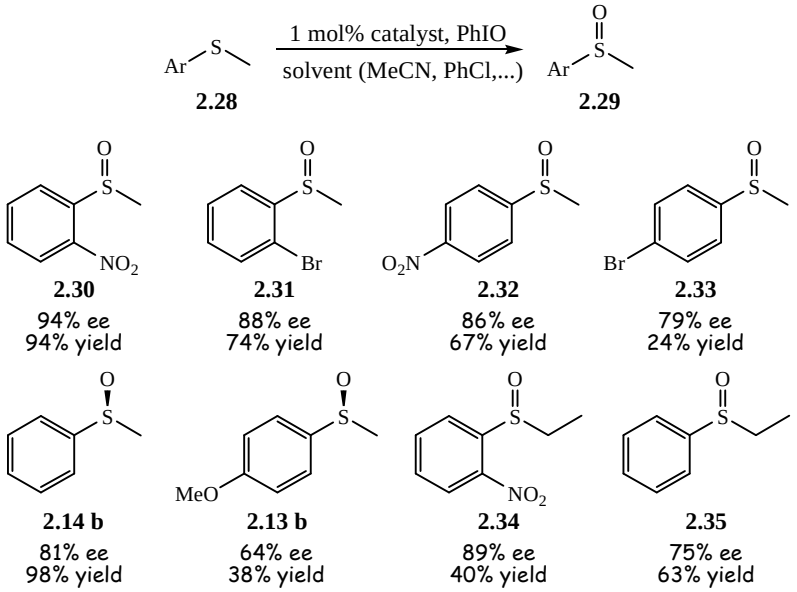
[101] a. Naruta Y.; Tani F.; Maruyama K. *J. Chem. Soc., Chem. Commun.* **1990**, 1378; b. Naruta Y.; Tani F.; Maruyama K. *Tetrhedron: Asymmetry* **1991**, *2(7)*, 533; c. Groves J. T.; Viski P. *J. Org. Chem.* **1990**, *55*, 3628 ; d. Halterman R. L.; Jan S.-T.; Nimmons H. L. *Synlett* **1991**, 791; e. Chiang L.; Konishi K.; Aida T.; Inoue S. *J. Chem. Soc., Chem. Commun.* **1992**, 255

[102] a. Palucki M.; Hanson P.; Jacobsen E. N. *Tetrahedron Lett.* **1992**, *33*, 7111 ; b. Noda K.; Hosoya N.; Irie R.; Yamashita Y.; Katsuki T. *Tetrahedron* **1994**, *50(32)*, 9609; c. Noda K.; Hosoya N.; Yanai K.; Irie R.; Katsuki T. *Tetrahedron Lett.* **1994**, *35(12)*, 1887; d. Kokubo C.; Katsuki T. *Tetrahedron* **1996**, *52(44)*, 13895



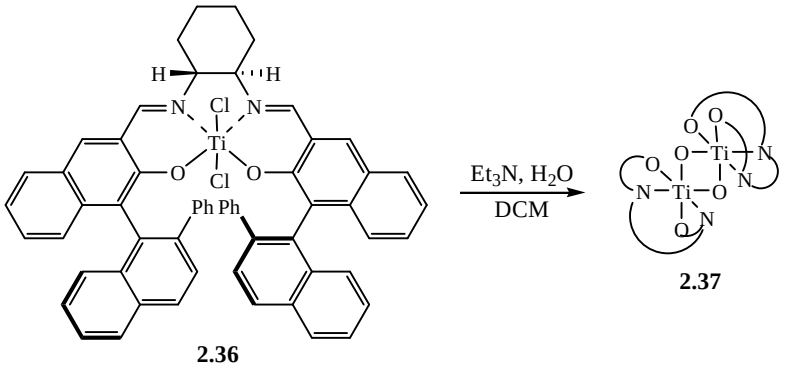
Scheme 68

While only moderate asymmetric inductions have been achieved with Jacobsen's catalyst, Katsuki obtained aryl methyl sulfoxides with up to *94%* enantioselectivity. Once again, aryl ethyl sulfides were oxidized in considerably lower optical purity. Substrates bearing electron withdrawing aromatic substituents were shown to be ideal candidates, resulting in high asymmetric induction. Furthermore, the formation of sulfone was suppressed by the addition of pyridine *N*-oxide or by carrying out the reaction at -20°C. Examples of their best results are presented in *Scheme 69*.



Scheme 69

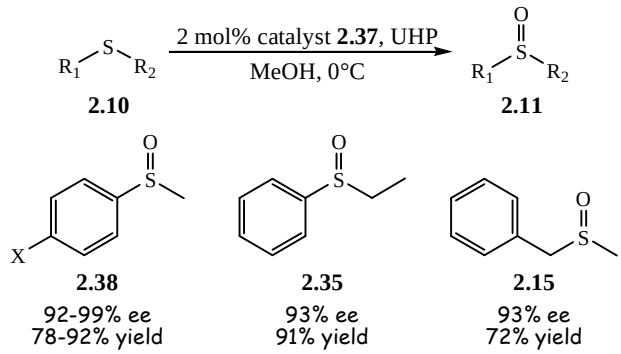
Katsuki tested other metals as well, in combination with his second generation ligands. Slightly better results were obtained in some cases by replacing the manganese by niobium.[103] Moreover, significantly higher asymmetric induction has been achieved using the dimeric μ-oxo titanium derivative **2.37** (*Scheme 70*).[104]



Scheme 70

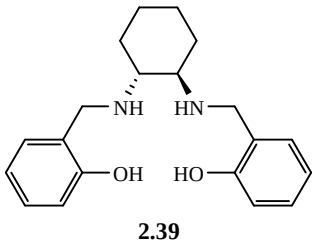
[103] Miyazaki T.; Katsuki T. *Synlett* **2003**, *7*, 1046
[104] Saito B.; Katsuki T. *Tetrahedron Lett.* **2001**, *42*, 3873

Using this new catalyst in the presence of urea hydroperoxide as terminal oxidant, high asymmetric induction has been achieved, not only for different aryl methyl sulfides, but also for phenyl ethyl and benzyl methyl substituted substrates (*Scheme 71*).



Scheme 71

Only moderate enantioselectivities have been achieved with other titanium or vanadium salen complexes.[105] Interestingly, the vanadium complex of the chiral salan ligand **2.39** showed superior results to its salen analogue in terms of reactivity and asymmetric induction.[106]



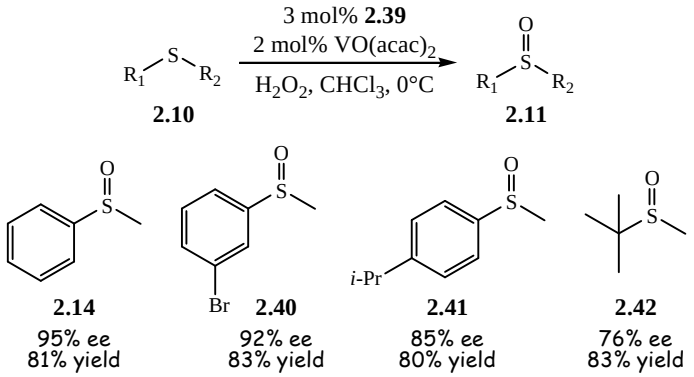
2.39

Scheme 72

[105] Ti: a. Colonna S.; Manfredi A.; Spadoni M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 71; b. Sasaki C.; Nakajima K.; Kojima M.; Fujita J. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1318; V: a. Nakajima K.; Kojima M.; Fujita J. *Chem. Lett.* **1986**, 1483; b. Nakajima K.; Kojima K.; Kojima M.; Fujita J. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2620

[106] Sun J.; Zhu C.; Dai Z.; Yang M.; Pan Y.; Hu H. *J. Org. Chem.* **2004**, *69*, 8500

Additionally, sulfoxides were obtained with opposite configuration and bulky ligand substituents on the phenol rings were detrimental to the enantioselectivity. The best results obtained with this catalytic system are presented in the scheme below.

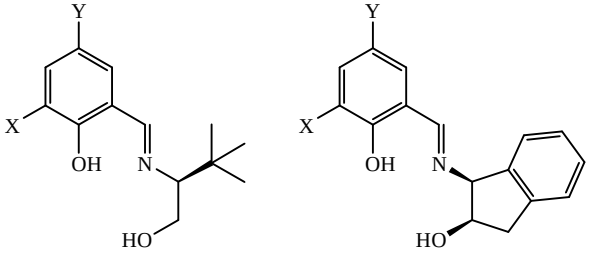


Scheme 73

In 1995, a new type of Schiff base ligand with O/N/O coordination property has been introduced by Bolm for vanadium(IV) catalyzed asymmetric sulfoxidation.[107] Since then, he and several other research groups tried to improve the ligand structure.[108] Huge libraries were built up with combination of differently substituted salicylaldehydes, sometimes bearing an additional central, planar or axial chirality, and chiral amino alcohols, such as (*S*)-*tert*-leucinol or (1*R*, 2*S*)-*cis*-aminoindanol. Their general structures are represented in *Scheme 74*.

[107] a. Bolm C.; Bienewald F. *Angew. Chem. Int. Ed. Engl.* **1995**, *34(23/24)*, 2640; b. Bolm C.; Schlingloff G.; Bienewald F. *J. Mol. Catal. A: Chem.* **1997**, *117*, 347

[108] a. Bolm C.; Bienewald F. *Synlett* **1998**, 1327; b. Vetter A. H.; Berkessel A. *Tetrahedron Lett.* **1998**, *39*, 1741; c. Skarżewski J.; Ostrycharz E.; Siedlecka R. *Tetrahedron: Asymmetry* **1999**, *10*, 3457; d. Ohta C.; Shimizu H.; Kondo A.; Katsuki T. *Synlett* **2002**, *1*, 161; e. Pelotier B.; Anson M. S.; Campbell I. B.; Macdonald S. J. F.; Priem G. *Synlett* **2002**, *7*, 1055

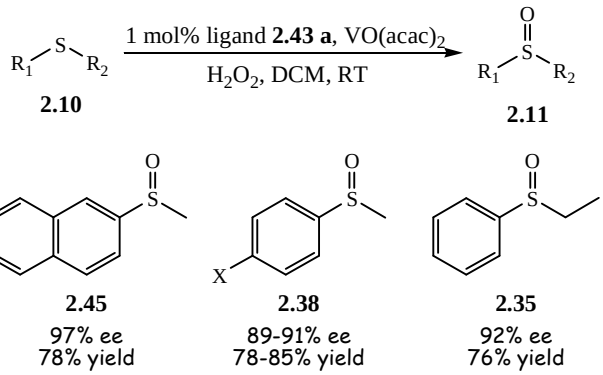


2.43 **2.44**

2.43 a: X=Y=I

Scheme 74

Up to now, the highest asymmetric inductions have been achieved with ligand **2.43 a**, bearing two iodo-substituents on the aromatic ring. Representative examples of the best results using this ligand are presented in *Scheme 75*.



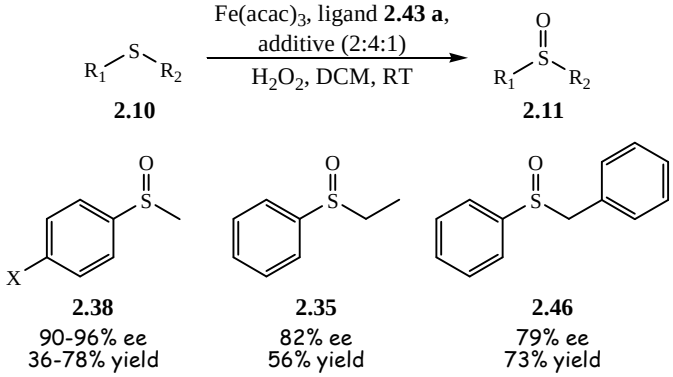
Scheme 75

Mechanistic investigations suggest the presence of chiral mononuclear vanadium(V)-monoperoxo complexes of different geometry as well as a small amount of achiral diperoxo vanadium(V) species.[109] Furthermore, it was suggested that the concentration of this

[109] a. Karpyshev N. N.; Yakovleva O. D.; Talsi E. P.; Bryliakov K. P.; Tolstikova O. V.; Tolstikov A. G. *J. Mol. Catal. A: Chem.* **2000**, *157*, 91; b. Bryliakov K. P.; Karpyshev N. N.; Fominsky S. A.; Tolstikov A. G.; Talsi E. P. *J. Mol. Catal. A: Chem.* **2001**, *171*, 73

latter, detrimental species should be kept at a low level by the slow addition of the oxidant.

The same ligand substitution pattern proved to be the best for iron(III) catalyzed sulfoxidations.[110] In this case the highest enantioselectivities were achieved in the presence of an additional benzoic acid or carboxylate ligand. The yields are generally lower as compared to the corresponding vanadium complexes, but the asymmetric induction is higher for certain substrates.



Scheme 76

As can be seen, remarkable results have been achieved in the field of asymmetric sulfoxidation using organometallic complexes of Schiff base ligands as catalysts. However, until now, high enantioselectivity combined with good chemical yield remained limited to a narrow range of substrates.

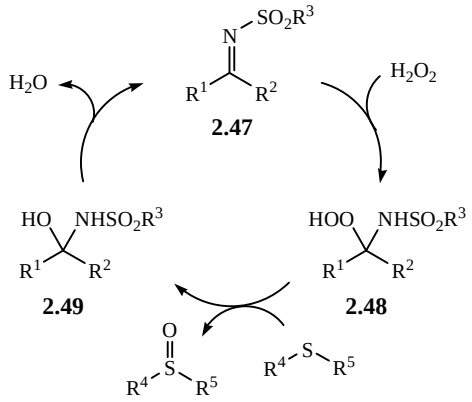
II. 6. Other asymmetric oxidizing systems

Several other systems, such as the use of chiral hydroperoxides or of electrochemistry on (polyamino acid)-coated electrodes, gave

[110] a. Bolm C.; Legros J. *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 5487; b. Bolm C.; Legros J. *Angew. Chem. Int. Ed. Engl.* **2004**, *43*, 4225; c. Legros J.; Bolm C. *Chem. Eur. J.* **2005**, *11*, 1086

promising results in asymmetric sulfoxidation. However, much work is still needed before they become really practical.[111]

Chiral sulfonyl oxaziridines are expected to be potential candidates as well. Since they gave encouraging results under stoichiometric conditions, one could imagine creating a catalytic system in which the oxaziridine is formed *in situ* from the chiral imine precursor. Page published the asymmetric oxidation of sulfides by the use of chiral sulfonimines. Unfortunately, very poor enantioselectivities were achieved under sub-stoichiometric conditions.[112] It is interesting to note that he proposed the formation of an α-hydroperoxyamine intermediate as the active catalytic species (*Scheme 77*), based upon the observation that the corresponding oxaziridines gave the opposite sense of asymmetric induction.



Scheme 77

[111] a. Mostowicz D.; Jurczak M.; Hamann H-J.; Höft E.; Chmielewski M. *Eur. J. Org. Chem.* **1998**, 2617; b. Adam W.; Korb M. N. Roschmann K. J.; Saha-Möller C. R. *J. Org. Chem.* **1998**, *63*, 3423; c. Komori T.; Nonaka T. *J. Am. Chem. Soc*. **1984**, *106*, 2656

[112] a. Page P. C. B.; Heer J. P.; Bethell D.; Collington E. W.; Andrews D. M. *Tetrahedron Lett.* **1994**, *35(51)*, 9629; b. Page P. C. B.; Heer J. P.; Bethell D.; Collington E. W.; Andrews D. M. *Synlett* **1995**, 773; c. Bethell D.; Page P. C. B.; Vahedi H. *J. Org. Chem.* **2000**, *65*, 6756

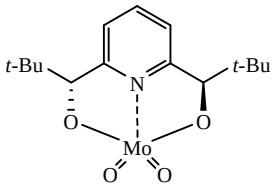
III. Objectives and preliminary results

Asymmetric epoxidation and sulfoxidation proved to be a very challenging area in organic synthesis. After the remarkable success of Sharpless, Jacobsen and Shi, asymmetric organic synthesis still requires catalysts that are not restricted to a given type of olefin. Similarly, the discovered titanium, vanadium, manganese and iron complexes used for catalytic asymmetric sulfoxidation give remarkable results only with a narrow range of substrates bearing suitable substituents. Furthermore, in both cases, the combination of high catalytic activity and high enantioselectivity is very rarely achieved. The discovery of new catalysts owning the combination of high activity, high enantioselectivity and applicability on a wide range of substrates is still required.

A few years ago, our laboratory began to work on the preparation of new organometallic catalysts suitable for the above mentioned transformations. Our research has been focused on molybdenum and vanadium catalysts bearing three dentate O/N/O type ligands, in which the nitrogen is part of a pyridine ring.

In fact, we were inspired by the fascinating structure of a molybdenum complex prepared in a simple ligand exchange reaction between $MoO_2(acac)_2$ and a pyridine diol by Sharpless *et al*. (*Scheme 78*).[113] Interestingly, in homochiral **3.1**, the usually hexacoordinated molybdenum was shown to be pentacoordinated. We envisioned that the empty coordination space of such a chiral complex would be ideal as a reaction site for an asymmetric transformation.

[113] Hawkins J. M.; Dewan J. C.; Sharpless K. B. *Inorg. Chem.* **1986**, *25*, 1501



3.1

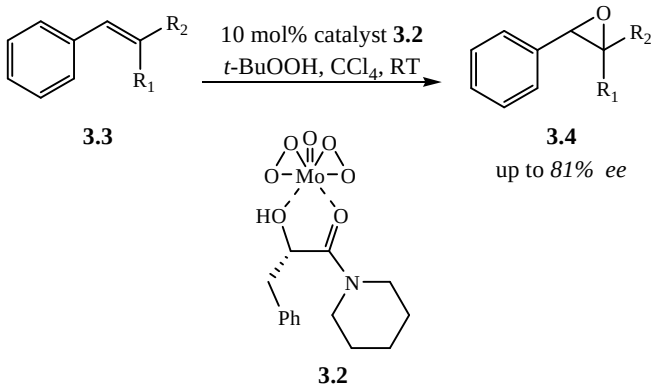
Scheme 78

Molybdenum is known to be an efficient catalyst for sulphur oxidation and alkene epoxidation. Molybdenum-catalyzed epoxidation of propylene with alkyl hydroperoxides became an important industrial process for the preparation of propylene oxide.[114] Nature also employs this metal centre in oxotransferase enzymes.[115] Additionally, it is stated that molybdenum is less toxic than manganese.[116] Despite these facts, molybdenum stayed behind titanium, manganese or vanadium in the plethora of studies dedicated to asymmetric catalysis. Recently, however, an increasing number of molybdenum(VI) oxo-, and peroxo-complexes, bearing chiral ligands, have been prepared and some of them have been tested in asymmetric oxidations.

Mimoun-type chiral peroxo-complexes, owning the $MoO(O_2)L_n$ general structure, are usually used as stoichiometric oxidants in the epoxidation of olefins.[117] The epoxides were obtained with low to moderate enantioselectivity. As far as we know, Yoon *et al.* published the first and, until now, the only remarkable report about

[114] a. Sheng M. N.; Zajacek J. G. (Atlantic Richfield Company) GB 1.136.923 **1968**; b. Kollar J. (Halcon International, Inc.) US 3.351.635 **1967**
[115] Hille R. *Chem. Rev.* **1996**, *96*, 2757
[116] Barlan A. U.; Basak A.; Yamamoto H. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 5849
[117] First application: Kagan H. B.; Mimoun H.; Mark C.; Schurig V. *Angew. Chem. Int. Ed. Engl.* **1979**, *18(6)*, 485

the catalytic use of such complexes.[118] Employing catalyst **3.2**, in the presence of *tert*-butyl hydroperoxide as the stoichiometric oxidant styrene derivatives could be oxidized in moderate yield and up to *81%* enantioselectivity.

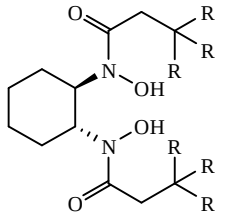


Scheme 79

Significantly more reports can be found in the literature on the catalytic use of molybdenum(VI) oxo-complexes bearing chiral ligands such as optically active diols, 2'-pyridinyl alcohols, oxazolines or Schiff bases.[119] Using organic hydroperoxides as stoichiometric oxidizing agents, these organometallic catalysts display generally good activity in the epoxidation of non-activated alkenes. However, the enantioselectivity of the product rarely exceeds *30%*. Interestingly, a few recent results appear to suggest that suitable ligand structures for highly enantioselective molybdenum catalysis are within reach. Yamamoto published that good enantioselectivities can be achieved in the oxidation of mono-, di-, and trisubstituted olefins using

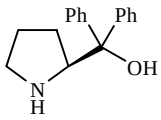
[118] Park S-W.; Kim K-J.; Yoon S. S. *Bull. Korean Chem. Soc.* **2000**, *21(4)*, 446
[119] Review: Kühn F. E.; Zhao J.; Herrmann W. A. *Tetrahedron: Asymmetry* **2005**, *16*, 3469

molybdenum complexes containing bishydroxamic acid ligands **3.5**.[120] The enantioselectivity of the epoxidation was over *90%* for conjugated disubstituted *cis* alkenes. Additionally, aryl alkyl sulfides were oxidized up to *86%* ee with these complexes. It is noteworthy that the corresponding vanadium complex gave high enantioselectivities only in the epoxidation of allylic and homoallylic alcohols.[121] A further encouraging example of asymmetric molybdenum catalysis is the epoxidation of monosubstituted styrenes with up to *84%* enantioselectivity using amino alcohol **3.6** as ligand, as published by Zhou.[122] Both Yamamoto and Zhou used $MoO_2(acac)_2$ as the precursor. However, the exact structures of their complexes are not known. Yamamoto found that a 2:1 ligand:molybdenum ratio is ideal for sulfoxidation, in contrast to a 1:1 for epoxidation. Furthermore, Zhou showed that increasing the ligand:molybdenum ratio from 1:1 to 2:1 in his epoxidation system, led to a considerable decrease in enantioselectivity.



R = phenyl, 4-alkyl-phenyl

3.5



3.6

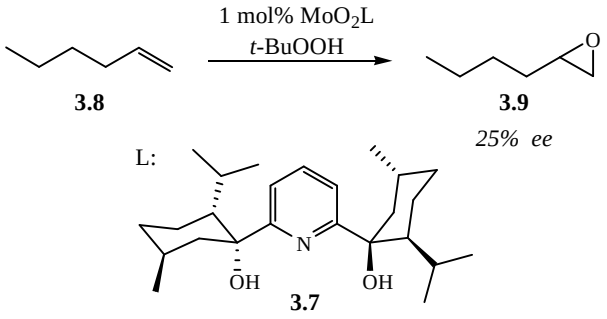
Scheme 80

[120] a. Barlan A. U.; Basak A.; Yamamoto H. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 5849; b. Basak A.; Barlan A. U.; Yamamoto H. *Tetrahedron: Asymmetry* **2006**, *17*, 508; c. Barlan A. U.; Zhang W.; Yamamoto H. *Tetrahedron* **2007**, *63*, 6075

[121] a. Zhang W.; Basak A.; Kosugi Y.; Hoshino Y.; Yamamoto H. *Angew. Chem. Int. Ed. Engl.* **2005**, *44*, 4389; b. Zhang W.; Yamamoto H. *J. Am. Chem. Soc.* **2007**, *129*, 286

[122] Wang Y.; Wu Z.; Li Z.; Zhou X-G. *Tetrahedron Lett.* **2009**, *50*, 2509

In the literature, we can find only a few examples of chiral molybdenum complexes bearing three dentate O/N/O type ligands. Osborn presented the five-coordinate C_2 symmetric MoO_2L type complex of ligand **3.7**.[123] He stated that this complex is monomeric in solution, and probably polymeric in the solid state. The X-ray structure of the crystalline complex showed dimers, weakly associated by two Mo=O···Mo interactions. This complex gave up to *25%* enantioselectivity in the epoxidation of 1-hexene (*Scheme 81*).

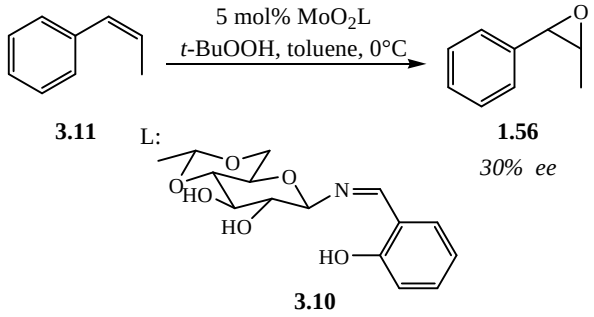


Scheme 81

Additionally, sugar derived chiral Schiff-bases such as **3.10** have also been reported as three dentate O/N/O type ligands of molybdenum dioxo complexes.[124] These complexes were prepared in methanol or ethanol, and a solvent molecule was found at the sixth coordination site of the metal centre. Nevertheless, this solvent molecule is supposed to be easily replaceable, being at a higher distance compared to the other coordinating atoms. Up to *30%* enantioselectivity has been achieved using **3.10** as ligand in the epoxidation of *cis-β*-methylstyrene (*Scheme 82*).

[123] Bellemin-Laponnaz S.; Coleman K. S.; Dierkes P.; Masson J-P.; Osborn J. A. *Eur. J. Inorg. Chem.* **2000**, 1645

[124] a. Sah A. K.; Rao C. P.; Saarenketo P. K.; Wegelius E. K.; Kolehmainen E. ; Rissanen K. *Eur. J. Inorg. Chem.* **2001**, 2773; b. Zhao J.; Zhou X.; Santos A. M.; Herdtweck E.; Romão C. C.; Kühn F. E. *Dalton Trans.* **2003**, 3736



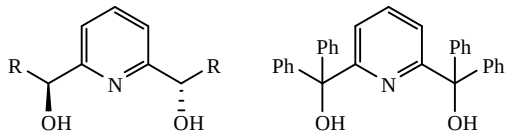
Scheme 82

Earlier to that, researchers of our laboratory prepared and tested several molybdenum complexes bearing differently substituted pyridine diol ligands.[125] Additionally, motivated by Bolm's results in asymmetric sulfoxidation using O/N/O type Schiff based ligands, the related vanadium complexes have been tested as well.[126] Our molybdenum and vanadium catalysts were prepared by ligand exchange reactions using the corresponding acetylacetonate complexes as precursors. The formed oxo-complexes were isolated before testing them in the oxidation of alkenes and sulfides. Generally, in the oxidation experiments, organic hydroperoxides were used as stoichiometric oxidants.

Our first generation molybdenum and vanadium oxo complexes, bearing ligands such as **3.12**, were found to be efficient in the oxidation of sulfides and in the epoxidation of electron rich alkenes. However, no enantiomeric excess was obtained using complexes containing the enantiopure ligands. These results were in accordance with the observations of Sharpless using his optically pure

[125] Tsukazaki M.; Phillipson N.; Markó I. E. *unpublished results*
[126] For details about Bolm's oxidation system see the previous chapter.

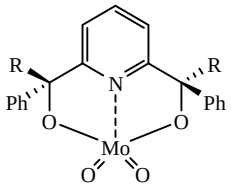
molybdenum complex **3.1** for the epoxidation of allylic alcohols.[127] Additionally, in the case of our vanadium catalyst, a long induction period has been observed in the epoxidation reactions, suggesting some degree of oxidation of the ligand.



3.12 **3.13**

Scheme 83

In stark contrast, vanadium complex of **3.13** proved to be recoverable and reusable, proving the oxidative stability of this more substituted ligand. Unfortunately, asymmetric versions of this second generation vanadium complexes couldn't be studied due to isolation and purification problems. On the other hand, the **3.14 a** and **3.14 b** asymmetric molybdenum complexes were isolated, purified and their structures were confirmed by X-ray analysis. Again, these recoverable and reusable catalysts didn't introduce asymmetry, either in the tested epoxidations or sulfoxidations.



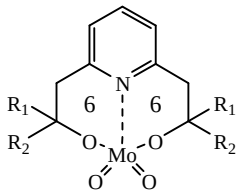
3.14 a R = Et
3.14 b R= 2,4,6-trimethylphenyl

Scheme 84

Based on the X-ray structures, it has been concluded that the chiral centres are probably too far from the site of oxidation in these

[127] Hawkins J. M.; Sharpless K. B. *Tetrahedron Lett.* **1987**, *28(25)*, 2825

complexes. Consequently, structure **3.15** has been suggested for the ideal distance between reaction site and chirality. This latter proposal was supported by the X-ray analysis of related complexes studied earlier by Holm.[128] However, the six-membered rings present in the structure were thought to be too flexible to introduce asymmetry.



3.15

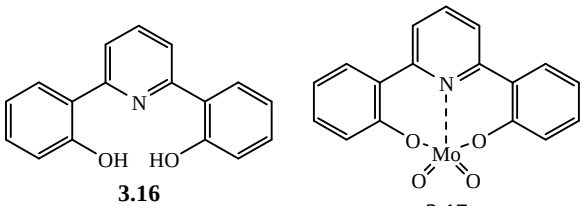
Scheme 85

Arriving at the subject of this thesis, the diaryloxypyridine ligand skeleton **3.16** has been proposed to rigidify these six-membered rings and the chirality was planned to be introduced at the phenol rings. Studies on the achiral ligand skeleton **3.16** started with Maristella Bernini, who found molybdenum complex **3.17** to be the most efficient oxidation catalyst as compared to our previously tested complexes.[129]

As far as we know, only boron complex of **3.16** has been prepared previously for its interesting electroluminescent property.[130] More recently, the formation of the corresponding aluminium(III), iron(III) and copper(II) complexes has been studied.[131] Furthermore, closely related ligands have been applied in zirconium(IV) and

[128] a. Berg J. M.; Holm R. H. *J. Am. Chem. Soc.* **1984**, *106*, 3035; b. Berg J. M.; Holm R. H. *J. Am. Chem. Soc.* **1985**, *107*, 917
[129] Bernini M.; Markó I. E. *unpublished results*; Patent demand (Rhodia) FR 2 826 595
[130] Li Y.; Liu Y.; Bu W.; Guo J.; Wang Y. *Chem. Commun.* **2000**, 1551
[131] Steinhauser S.; Heinz U.; Sander J.; Hegetschweiler K. *Z. Anorg. Allg. Chem.* **2004**, *630*, 1829

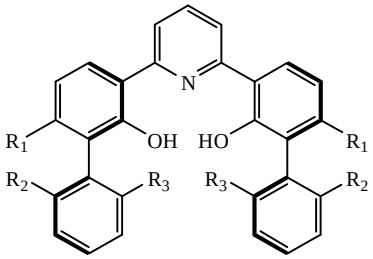
titanium(IV) catalyzed polymerization of ethylene or as highly selective beryllium(II) chelating agent.[132]



3.16 **3.17**

Scheme 86

The main objective of the present thesis was to extend our study to diaryloxypyridine ligands **3.18**, bearing axial chirality on the phenol fragments.



3.18

Scheme 87

In the following chapters, the synthesis of **3.16** and achiral models of the planned chiral ligands will be presented first. Then, the preparation, isolation and characterization of the corresponding molybdenum complexes will be described, followed by a structure-activity relationship study of these complexes. The application of the established synthetic strategy to the preparation of different chiral ligands and related molybdenum complexes, as well as the study of

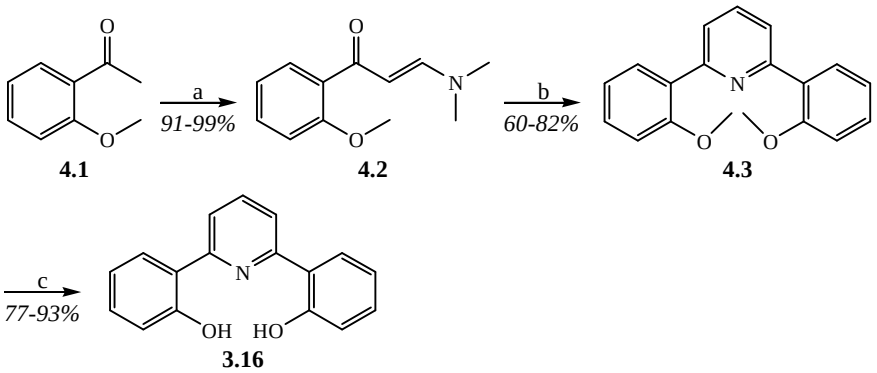
[132] a. Chan M. C. W.; Tam K-H.; Pui Y-L.; Zhu N. *J. Chem. Soc. Dalton Trans.* **2002**, 3085; b. Matsumiya H.; Hoshino H. *Anal. Chem.* **2003**, *75(3)*, 413

these new chiral organometallic catalysts in epoxidation and sulfoxidation reactions will be exposed afterwards.

IV. Synthesis of achiral ligands

IV. 1. Synthesis of the simple diaryloxy-pyridine, ligand 3.16

First of all, we carried out the synthesis of ligand **3.16** based on a published method (*Scheme 88*).[133] The procedure begins with the formation of enaminone **4.2** from the corresponding commercially available ketone **4.1**. As the key step, ketone **4.1** and its enaminone derivative **4.2** are reacted in the presence of base to form a Michael adduct, which is then reacted further with ammonium acetate, under acidic conditions to form the pyridine ring. Finally, cleavage of the two methoxy groups is carried out with molten pyridinium hydrochloride.



a) $Me_2NCH(OMe)_2$, 110°C, 24h; b) i. 1 eq. **4.1**, 2 eq. base, THF, RT, 15 min.; ii. 2 eq. **4.2**, RT, 24h; iii. NH_4OAc, AcOH, 110°C, 2h; c) 40 eq. Pyridinium.HCl, 210°C, 2h.

Scheme 88

In order to increase the yield, the reaction conditions of the key step were modified by our group.[134] It was found that using sodium hydride as a base instead of potassium *tert*-butoxide led to improved

[133] Silva A. M. S.; Almeida L. M. P. M.; Cavaleiro J. A. S. *Tetrahedron* **1997**, *53(34)*, 11645
[134] Bernini M.; Markó I. E. *unpublished results*

conversions. Moreover, the amount of enaminone could be decreased by half (*Table 1*).

Entry	Base	Enaminone	*Yield*
1[*]	*t*-BuOK	4 eq.	*60%*
2	NaH	2 eq.	*82%*

*literature result

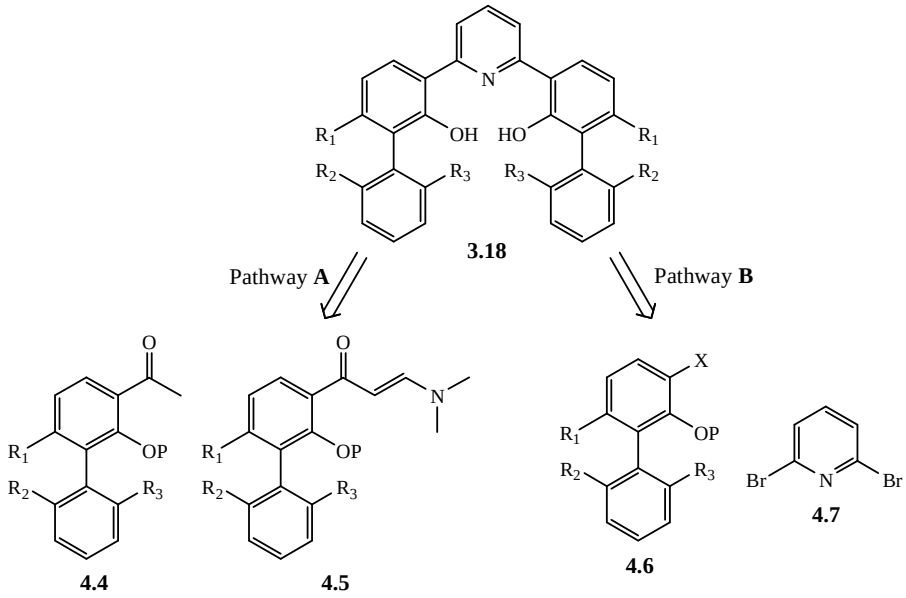
Table 1

Using this method, excellent yields were obtained for all steps of the diaryloxy-pyridine skeleton formation. However, it has to be pointed out that the synthesis would be much more convergent if two identical 2-methoxyphenyl fragments were used in the key step. Additionally, in the case of our target ligands bearing axial chirality, high temperature conditions might cause racemisation. Alternative synthetic pathways, as well as optimization of reaction conditions, in which the simple diaryloxy-pyridine ligand has been used as model, will be detailed in the following chapters.

IV. 2. Synthesis of the symmetrically substituted diaryloxy-pyridine model

IV. 2. 1. Introduction

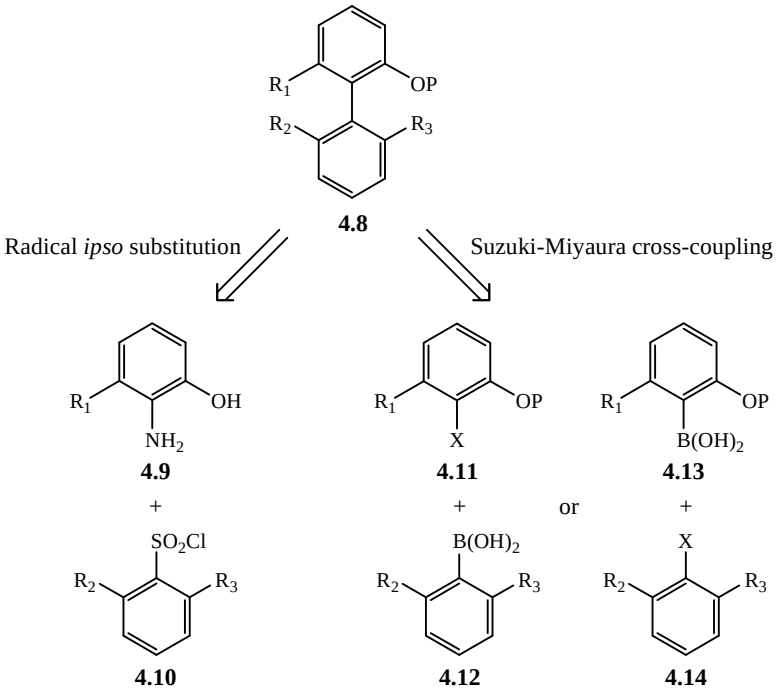
The synthesis of chiral ligands of type **3.18** has been investigated according to two different retrosynthetic pathways (*Scheme 89*). In the first one, the key step is the pyridine ring formation from a ketone and its enaminone derivative, as described before (*Pathway **A***). For the second route, the already existing pyridine ring is to be coupled with two identical biphenyl fragments (*Pathway **B***).



Scheme 89

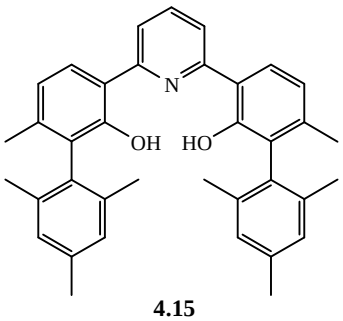
In both cases the starting materials are built up from the same biphenyl fragment **4.8**. Thus, in case of success, pathway **B** represents a much shorter and more convergent approach.

Two different methods have been suggested for the formation of the common biphenyl fragment as well. We planned to prepare **4.8** either *via* a three step procedure, which includes a radical mediated intramolecular *ipso* substitution, or by a Suzuki-Miyaura cross-coupling reaction (*Scheme 90*).



Scheme 90

Ligand **4.15** has been selected as a non-chiral model substrate to investigate the synthesis, and later on, to study the activity of the corresponding molybdenum catalyst.



4.15

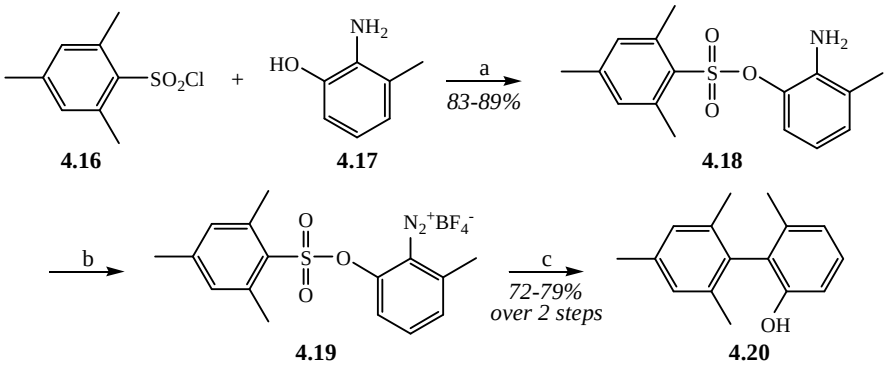
Scheme 91

In the next paragraphs, the formation of the corresponding biphenyl fragment by the two different methods will be presented first. Afterwards, the construction of the ligand core *via* pathway **A**,

then *via* pathway **B** will be detailed. And finally, our investigations about the cleavage of the hydroxyl protecting groups will be described.

IV. 2. 2. Formation of the hydroxy-biphenyl fragment via radical intramolecular ipso substitution

Synthesis of biaryls, fully hindered by *ortho*-substituents, is usually quite challenging. Thus, we were particularly pleased to find in the literature the brilliant method of Motherwell for the formation of our hydroxy-biphenyl fragment.[135] The procedure begins with the formation of sulfonate **4.18** from mesitylenesulfonyl chloride and 2-amino-*meta*-cresol in the presence of triethylamine (*Scheme 92*). Then, diazotation is carried out with isoamyl nitrite and tetrafluoroboric acid in ethanol. And finally, diazonium salt **4.19** is reacted with titanium(III)-chloride to generate a free radical which undergoes an intramolecular *ipso* substitution.

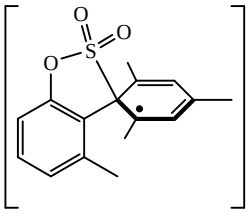


a) Et_3N, DCM, 0°C to RT; b) HBF_4, *i*-$C_5H_{11}ONO$, EtOH, 0°C; c) $TiCl_3$, $HCl_{(aq)}$, acetone, 0°C.

Scheme 92

[135] Bonfand E.; Forslund L.; Motherwell W. B.; Vàzquez S. *Synlett* **2000**, *4*, 475

The proposed structure of the spirocyclic intermediate, capable of rearomatization through loss of sulphur dioxide is shown below (*Scheme 93*).



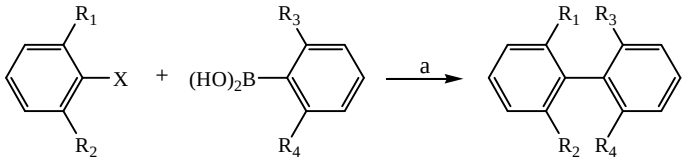
4.21

Scheme 93

Luckily, the *ipso* substitution is the most selective for fully hindered biaryls, and thus, hydroxy-biphenyl **4.20** was obtained in a good overall yield.

IV. 2. 3. Formation of the biphenyl fragment via Suzuki-Miyaura cross-coupling reaction

As mentioned above, the synthesis of sterically hindered, tetra-*ortho* substituted biphenyls is quite difficult in general. However, recently, remarkable results were published in this field by applying the Suzuki-Miyaura cross-coupling reaction (*Scheme 94*).[136]



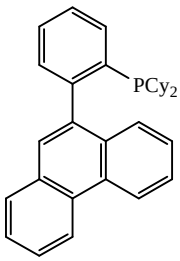
4.22 **4.23** **4.24**

a) Palladium catalyst, K_3PO_4, toluene, 110°C.

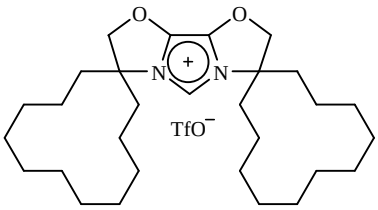
Scheme 94

[136] a. Yin J.; Rainka M. P.; Zhang X-X.; Buchwald S. L. *J. Am. Chem. Soc.* **2002**, *124(7)*, 1162; b. Altenhoff G.; Goddard R.; Lehmann C. W.; Glorius F. *J. Am. Chem. Soc.* **2004**, *126(46)*, 15195

Both Buchwald and Glorious demonstrated the need of bulky ligands to achieve such palladium catalyzed couplings. Interestingly, they applied the same solvent/base system, but the nature of their ligands was different. Sterically demanding phosphine **4.25** was used by Buchwald, and bioxazoline-derived N-heterocyclic carbene **4.26** by Glorious (*Scheme 95*).



4.25
Buchwald

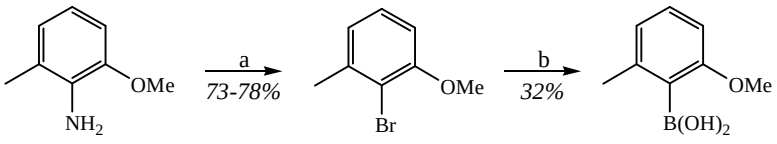


4.26
Glorious

Scheme 95

The promising results obtained by these research groups prompted us to test their catalytic system in the preparation of our biphenyl fragment.

We prepared the required starting materials from commercially available amine derivatives. Bromide **4.28** was obtained in good yield *via* a Sandmeyer reaction. A portion of this bromide was transformed successfully into the corresponding boronic acid **4.29** (*Scheme 96*).

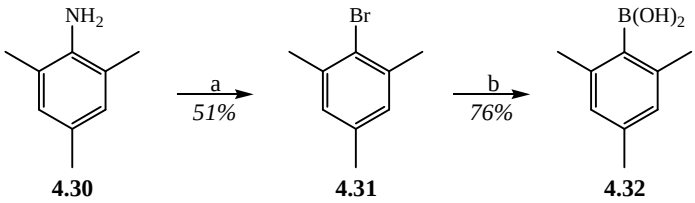


4.27 **4.28** **4.29**

a) i. $NaNO_2$, $HBr_{(aq.)}$, H_2O, 0°C; ii. CuBr, $HBr_{(aq.)}$, H_2O, 130°C; b) i. *n*-BuLi, THF, -78°C; ii. B(*i*-PrO)$_3$, -78°C to RT; iii. $HCl_{(aq.)}$, 0°C to RT.

Scheme 96

Similarly, we obtained bromide **4.31** and boronic acid **4.32** in good isolated yields (*Scheme 97*). At this stage, two different combinations of these bromides and boronic acids in the Suzuki-Miyaura coupling are possible that should enable us to obtain the desired biphenyl fragment **4.35**.

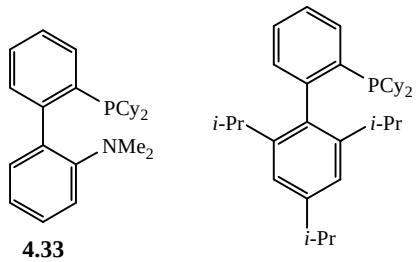


4.30 **4.31** **4.32**

a) i. $NaNO_2$, $HBr_{(aq.)}$, H_2O, 0°C; ii. CuBr, $HBr_{(aq.)}$, H_2O, 130°C; b) i. *n*-BuLi, THF, -78°C; ii. B(*i*-PrO)$_3$, -78°C to RT; iii. $HCl_{(aq.)}$, 0°C to RT.

Scheme 97

Unfortunately, neither the carbene of Glorious, nor the phenanthrene-based phosphine of Buchwald is commercially available. It was thus decided to test other bulky phosphine ligands furnished by Rhodia (*Scheme 98*). Among them, N-Phos **4.33** was reported as giving good results in the formation of highly hindered biaryls. These, like our substrate, possess a methoxy group as one of the *ortho*-substituents. We expected that using X-Phos **4.34** comparable results could be achieved.

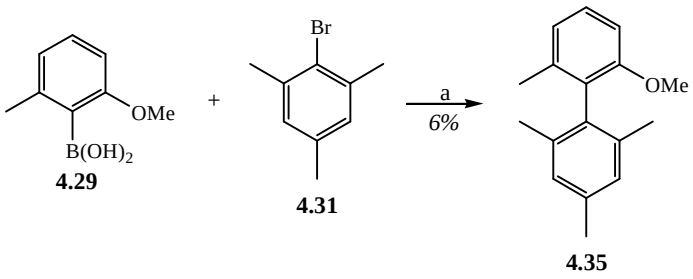


4.33
N-Phos

4.34
X-Phos

Scheme 98

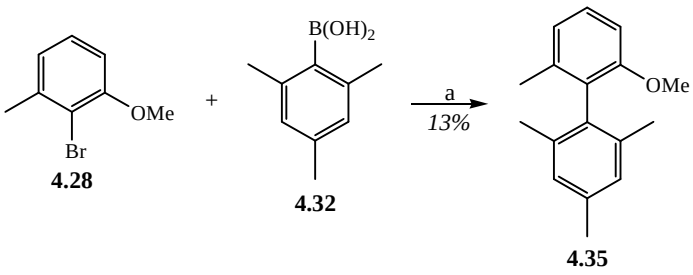
Initially, we tested the reaction between bromide **4.31** and boronic acid **4.29** (*Scheme 99*). Using X-Phos as ligand, we could obtain **4.35** in a very low yield. Similar results were achieved by using $Pd(OAc)_2$ or Pd_2dba_3 as the palladium source.



a) 4 mol% Pd_2dba_3, 8 mol% X-Phos, 2 eq. **4.29**, 3 eq. K_3PO_4, Toluene, 110°C.

Scheme 99

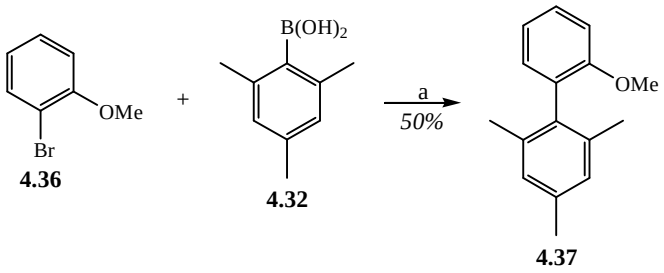
By switching the bromide and boronic acid fragments, **4.35** was formed in a somewhat better, though still unsatisfactory, yield (*Scheme 100*). Doubling the amount of the catalyst did not increase the yield of the reaction. Furthermore, using N-Phos as ligand provided inferior results.



a) 4 mol% Pd_2dba_3, 8 mol% X-Phos, 2 eq. **4.32**, 3 eq. K_3PO_4, Toluene, 110°C.

Scheme 100

To confirm that our lack of experience was not the reason of these disappointing results, we tested the formation of biphenyl **4.37** bearing only three *ortho*-substituents. To our delight, **4.37** was obtained in good yield under the same conditions (*Scheme 101*).



a) 4 mol% Pd_2dba_3, 8 mol% X-Phos, 2 eq. **4.32**, 3 eq. K_3PO_4, Toluene, 110°C.

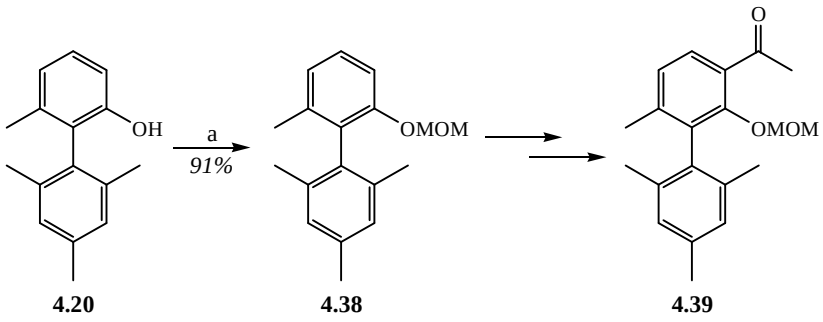
Scheme 101

Thus, our coupling conditions were not synthetically useful for the preparation of the fully hindered biphenyl fragment **4.35**. However, we could probably use this method for the assembly of ligands in which the axial rotation of the biphenyl fragment is blocked by only three *ortho*-substituents.

At that point, we still had the possibility to synthesize the original, fine-tuned ligand of Buchwald or Glorious for the formation of the tetra-*ortho*-substituted biphenyl fragment **4.35**. On the other hand, the method of Motherwell proved so effective that we decided to focus instead our attention on the formation of the diaryloxy-pyridine core.

IV. 2. 4. Synthesis of the ligand core via pyridine ring formation

With the hydroxy-biphenyl fragment **4.20** in hand, we continued the synthesis towards the formation of ketone **4.39**. Since cleavage of the methoxy groups required harsh conditions in the case of ligand **3.16**, we decided to change the hydroxyl protecting group. Hence, the methoxymethyl ether **4.38** was prepared in excellent yield by a classical procedure (*Scheme 102*).

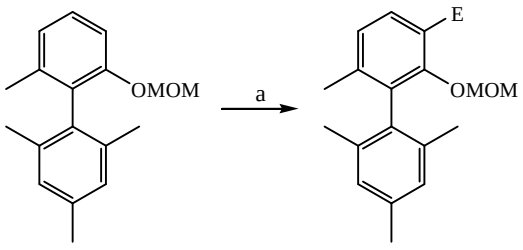


4.20 **4.38** **4.39**

a) NaH, MOMCl, THF, 0°C to RT.

Scheme 102

We planned to synthesize ketone **4.39** *via* the directed *ortho*-lithiation of **4.38**, followed by the addition of an acylating electrophile (*Scheme 103*). Unfortunately, neither acetic anhydride nor acetyl chloride gave the desired ketone **4.39**. Instead, the starting material was recovered. To confirm the formation of the *ortho*-lithiated species, other electophiles have been tested as well (*Table 2*).



4.38 **4.40**

a) BuLi, THF, -78°C to 0°C, then electrophile.

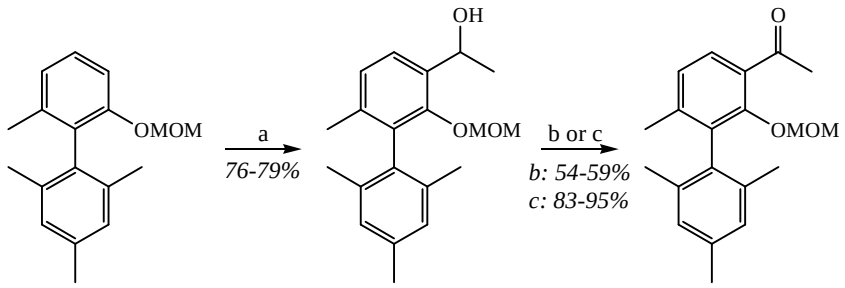
Scheme 103

Entry	Electrophile	*Result*
1	Ac_2O	*recovered starting material*
2	AcCl	*recovered starting material*
3	TMSCl	*complete conversion*
4	D_2O	*complete conversion*
5	CH_3CHO	*79% isolated yield*

Table 2

We were delighted to observe that complete conversions were achieved using trimethyl silyl chloride or deuterated water as electrophile. These experiments unambiguously demonstrated the formation of the *ortho*-lithiated intermediate. At this stage, we thought that if the carbonyl function is sterically less hindered than that of acetyl chloride or acetic anhydride, we will be able to capture the lithiated species. Satisfyingly, by adding acetaldehyde to the anion derived from **4.38** the corresponding alcohol **4.41** was obtained in a very good isolated yield (*Entry 5*).

The obtained alcohol **4.41** was then successfully oxidized to ketone **4.39** either by the $CuCl/O_2$ system developed in our laboratory or by manganese dioxide (*Scheme 104*).[137]



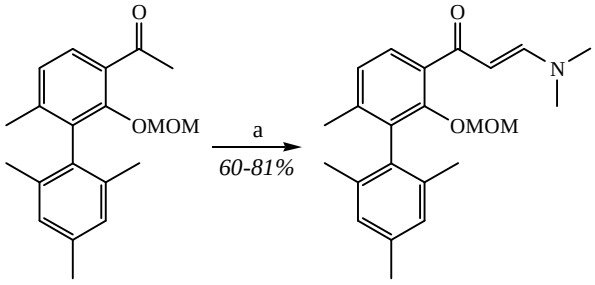
4.38 **4.41** **4.39**

a) *n*-BuLi, THF, -78°C to 0°C, then CH_3CHO; b) 5 mol% CuCl / 1,10-phenantroline / *t*-BuOK / DBAD, O_2, C_6H_5F, 80°C; c) MnO_2, DCM, RT.

Scheme 104

The transformation of ketone **4.39** into the corresponding enaminone **4.42** by the previously applied method proceeded smoothly (*Scheme 105*).

[137] a. Markó I. E.; Giles P. R.; Tsukazaki M.; Brown S. M.; Urch C. J. *Science* **1996**, *274*, 2044; b. Markó I. E.; Gautier A.; Mutonkole J-L.; Dumeunier R.; Ates A.; Urch C. J.; Brown S. M. *J. Organomet. Chem.* **2001**, *624*, 344

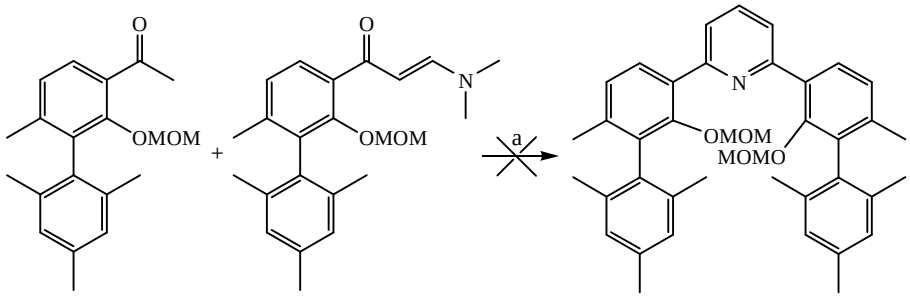


4.39 **4.42**

a) 2 eq. $Me_2NCH(OMe)_2$, 110°C, 24h.

Scheme 105

With both the ketone **4.39** and the enaminone **4.42** in hand, the key step of pathway **A** was attempted (*Scheme 106*). Initially, the ketone was reacted with sodium hydride, and then the enaminone was added to the mixture. After 24 hours stirring at room temperature, precipitation was not observed, in contrast to the previous experiments. Nevertheless, the procedure was continued as usual, and unfortunately, the desired product was not obtained.



4.39 **4.42** **4.43**

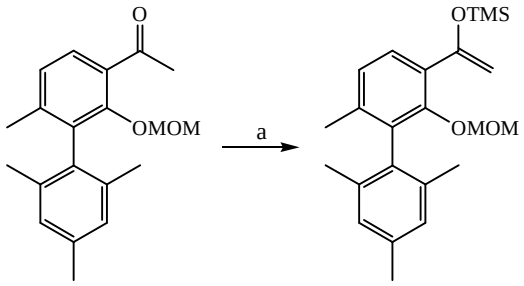
a) 2 eq. NaH, THF, RT, 24h, then NH_4OAc, AcOH, 110°C, 2h.

Scheme 106

Since the starting ketone **4.39** was recovered (partially deprotected due to the acidic conditions of the ring closing step) and the usual precipitate formation was not observed during the reaction, we concluded that the formation of the Michael adduct didn't occur. It

means that, either the enolate didn't form, or that the *in situ* generated enolate couldn't add to the enaminone. To determine the origin of our problem, we decided to study the formation of the enolate first.

Treating ketone **4.39** with sodium hydride under the usual reaction conditions, followed by the addition of trimethyl silyl chloride, did not lead to the formation of silyl enol ether **4.44** (*Scheme 107* and *Table 3*). However, using other bases, such as LDA or KHMDS at -78°C, high conversions could be obtained (*Entry 2 and 3*).



4.39 **4.44**

a) Base, then TMSCl.

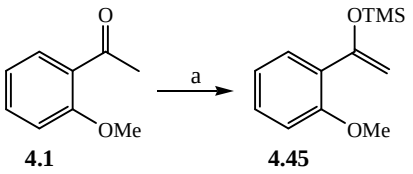
Scheme 107

Entry	Base	*Result*
1	NaH	*recovered starting material*
2	LDA	*complete conversion*
3	KHMDS	*high conversion*

Table 3

For comparison, the same test reactions were carried out with ketone **4.1** (*Scheme 108* and *Table 4*). Surprisingly, the results were very similar. Using sodium hydride as the base, the corresponding silyl enol ether **4.45** was not formed, even after prolonged reaction times and employing a more concentrated reaction medium. The

reason why this enolate can be trapped by the enaminone **4.2** and not by trimethyl silyl chloride is not fully understood at present.



4.1 **4.45**

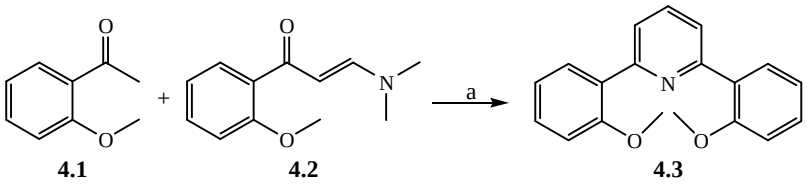
a) Base, then TMSCl.

Scheme 108

Entry	Base	*Result*
1	NaH	*recovered starting material*
2	LDA	*complete conversion*
3	KHMDS	*84% isolated yield*

Table 4

In view of these results, we tested KHMDS in the formation of **4.3** (*Scheme 109* and *Table 5*).



4.1 **4.2** **4.3**

a) Base, THF, -78°C to RT, 24h, then NH_4OAc, AcOH, 110°C, 2h.

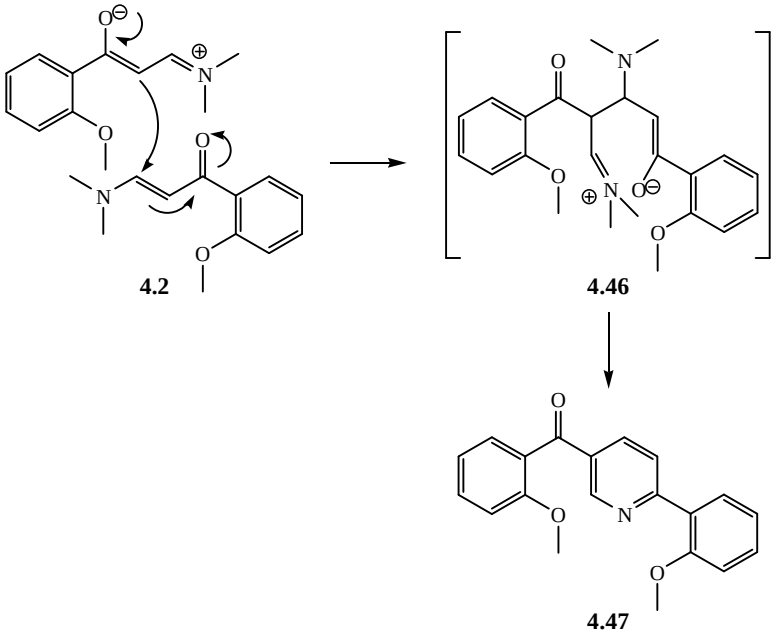
Scheme 109

Entry	Base	Enaminone	Concentration	*Yield*
1	2 eq. NaH	2 eq.	0.1 M	*82%*
2	2 eq. KHMDS	2 eq.	0.4 M	*54%*

Table 5

Compared to sodium hydride, KHMDS gave inferior results. It is possible that the addition of the enolate to the enaminone was less selective due to the higher concentration of the enolate. We have to mention, that the reaction concentration was also somewhat higher in

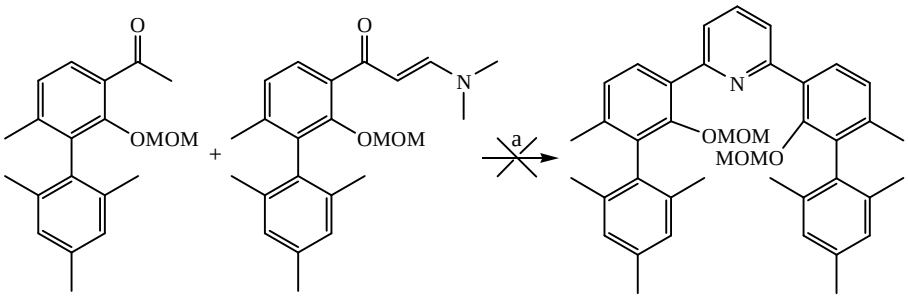
the latter case. We did not isolate and analyze the byproducts of the reaction, except **4.47** originating from the condensation of two enaminone molecules (*Scheme 110*).



Scheme 110

Later on, it has been confirmed that byproduct **4.47** forms as well when sodium hydride is used as the base, but in much lower amount.

Despite the competing side reactions, we decided to test this latter reaction condition for the synthesis of **4.43** (*Scheme 111*).

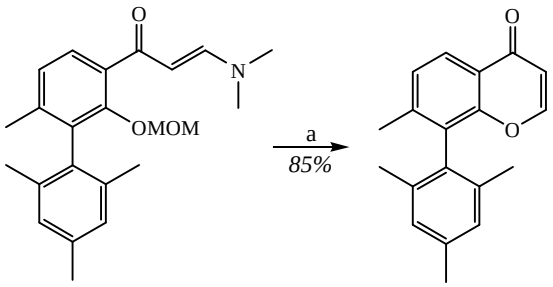


4.39 **4.42** **4.43**

a) 2 eq. KHMDS, THF, -78°C to RT, 24h, then NH_4OAc, AcOH, 110°C, 2h.

Scheme 111

Unfortunately, the required reaction didn't occur either under this condition. Besides some partially deprotected starting materials, we isolated also **4.48** from the reaction mixture. It has been proven later that this product forms from enaminone **4.42** upon heating under acidic conditions (*Scheme 112*). Hence, this side reaction is clearly not competitive with the desired process.

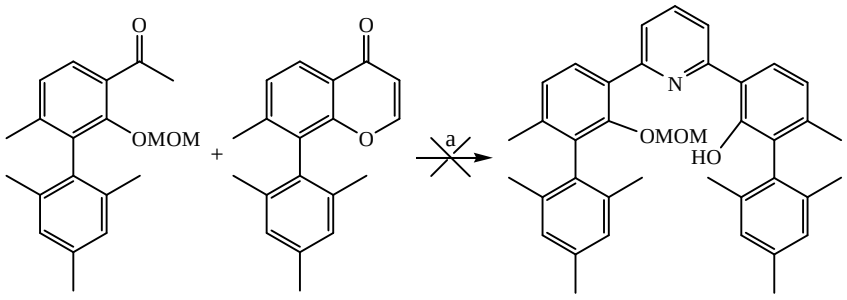


4.42 **4.48**

a) HCl, DCM, reflux, 2h.

Scheme 112

We attempted to use **4.48** instead of enaminone **4.42** in the ligand synthesis, hoping that the 4-chromenone ring can be re-opened by the enolate. But once again, we did not obtain the desired product (*Scheme 113*).

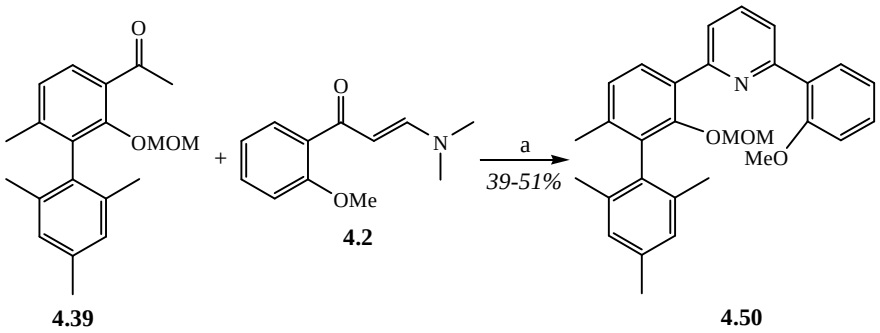


4.39 **4.48** **4.49**

a) 2 eq. NaH, THF, RT, 24h, then NH_4OAc, AcOH, 110°C, 2h.

Scheme 113

In view of the obtained results, we proposed that the *in situ* generated enolate doesn't add to enaminone **4.42** probably due to the steric hindrance of the coordinating MOM protecting group. However, before changing the protecting group, the reaction between ketone **4.39** and enaminone **4.2** was tested (*Scheme 114*).



4.39 **4.2** **4.50**

a) Base, THF, RT, 24h, then NH_4OAc, AcOH, 110°C, 2h.

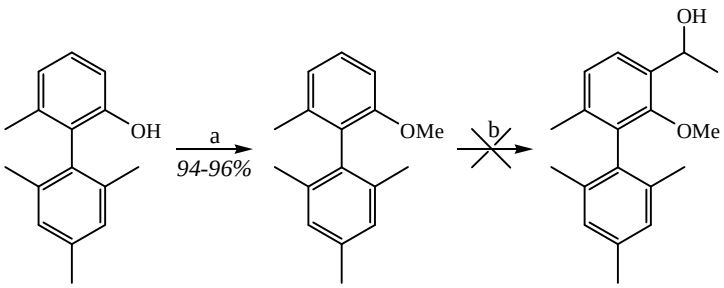
Scheme 114

Entry	Base	Enaminone	Concentration	*Yield*
1	2 eq. NaH	2 eq.	0.5 M	*51%*
2	2 eq. KHMDS	2 eq.	0.5 M	*49%*
3	2 eq. NaH	2 eq.	0.1 M	*39%*

Table 6

Much to our delight, the formation of the partially deprotected **4.50** was observed. It has to be pointed out that sodium hydride and KHMDS gave very similar results, and that decreasing the concentration of the reaction medium lowered the yield of the required product (*Table 6*). We did not try to find the optimal concentration for this reaction, but realized the opportunity to test the deprotected **4.50** as a ligand for molybdenum.

Concerning the synthesis of ligand **4.15**, we decided to change the protecting group of the hydroxyl function back to the original methoxy substituent. To obtain ketone **4.58**, the previously applied *ortho*-lithiation procedure was tried initially. Unfortunately, however, the methoxy ether **4.35** did not react under the same conditions.

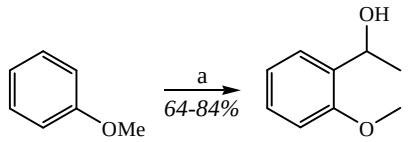


4.20 **4.35** **4.51**

a) MeI, KOH, DMSO, RT; b) *n*-BuLi, THF, -78°C to 0°C, then CH_3CHO.

Scheme 115

Methoxy group directed *ortho*-lithiations are known to be more difficult than methoxymethyl directed ones. However, when the same condition was tested using anisole **4.52** as the starting material, the corresponding alcohol was obtained in excellent yield (*Scheme 116*). It is possible that the electronic effects of the other substituents are not favourable for the lithiation of our substrate.



4.52 **4.53**

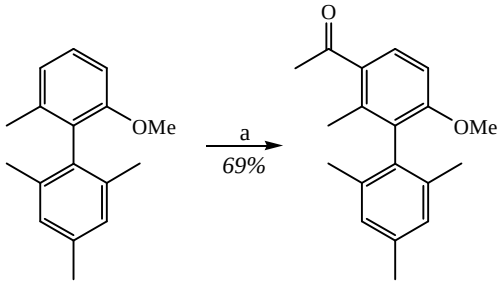
a) *n*-BuLi, THF, -78°C to 0°C, then CH_3CHO.

Scheme 116

Several other conditions were tested, using normal, secondary or tertiary butyl lithium as base, in the presence or absence of TMEDA, using THF or diethyl ether as the solvent, alas to no avail. The reaction temperature and concentration were varied as well and, besides acetaldehyde, other electrophiles such as TMSCl and deuterated water were used to quench the reaction. At that point, however, we could not find any conditions to carry out the *ortho*-lithiation of **4.35**.

Other methods were attempted to obtain ketone **4.58**, such as the Friedel-Crafts acylation or a Fries rearrangement. Based upon the substitution pattern of the aromatic ring bearing the methoxy functionality, we could expect the acylation to occur mainly *para* to the methoxy group. However, we wanted to see if the directing effect of the methyl substituent would be strong enough to obtain the desired ketone **4.58** as well in reasonable amount.

Unfortunately, the Friedel-Crafts acylation gave exclusively the unwanted regioisomer **4.54** under the conditions employed (*Scheme 117*).

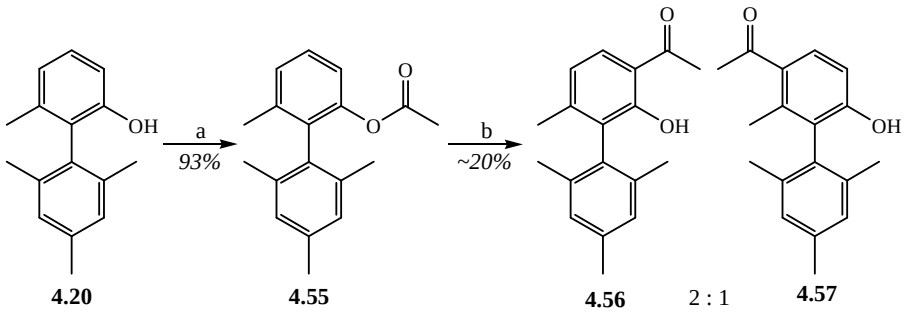


4.35 **4.54**

a) CH_3COCl, $SnCl_4$, DCM, 0°C.

Scheme 117

In stark contrast, the Fries-rearrangement of acetate **4.55** provided a 2:1 mixture of regioisomers in favour of the desired ketone (*Scheme 118*).



4.20 **4.55** **4.56** **4.57**

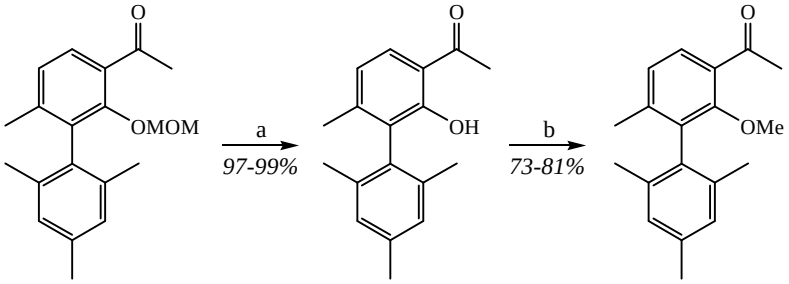
a) Et_3N, CH_3COCl, DCM, 0°C to RT; b) $AlCl_3$, PhCl, 140°C.

Scheme 118

Actually, in the Fries rearrangement of a phenolic ester in the presence of a Lewis acid, the displacement of the acetyl group *para* to the hydroxyl function is kinetically favoured. However, high temperature conditions promote the formation of the *ortho* isomer. Moreover, the Lewis acid catalyzes the rearrangement of the *para* isomer to the *ortho* one upon heating. Though the required regioisomer was formed in excess, the reaction conditions are not synthetically useful due to the rather low yield. Indeed, whilst the

starting acetate was fully consumed, the hydroxy-biphenyl **4.20** was formed as the main product.

In order to verify the viability of the subsequent steps of the synthesis, we didn't try to optimize the conditions of the Fries rearrangement, but directly prepared ketone **4.58** from **4.39** by a simple deprotection-protection procedure (*Scheme 119*).

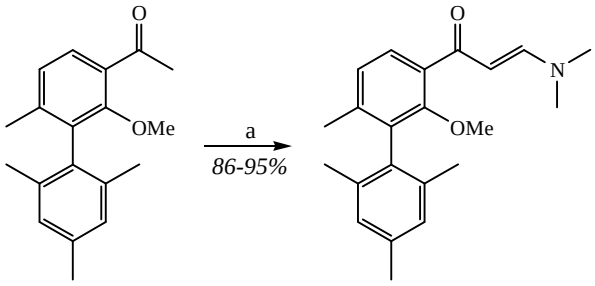


4.39 **4.56** **4.58**

a) cc. HCl, THF : *i*-PrOH 1:1; b) K_2CO_3, Me_2SO_4, acetone, reflux.

Scheme 119

The formation of enaminone **4.59**, by the previously described method, proceeded efficiently (*Scheme 120*).

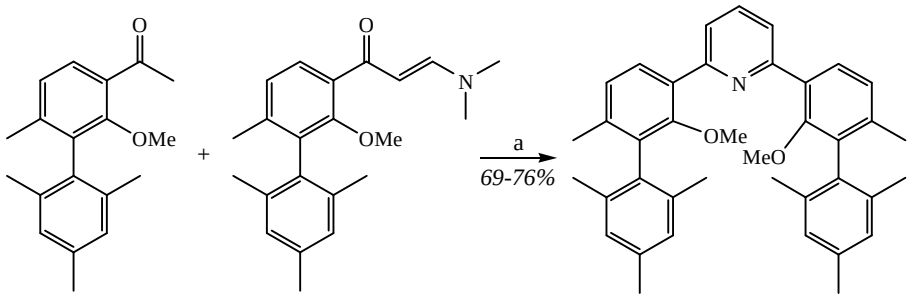


4.58 **4.59**

a) 2 eq. $Me_2NCH(OMe)_2$, 110°C, 24h.

Scheme 120

With ketone **4.58** and enaminone **4.59** in hand, the key step was next attempted. Much to our pleasure, the formation of **4.60** proceeded smoothly and in high yield (*Scheme 121*).



4.58 **4.59** **4.60**

a) 2 eq. NaH, THF, RT, 24h, then NH_4OAc, AcOH, 110°C, 2h.

Scheme 121

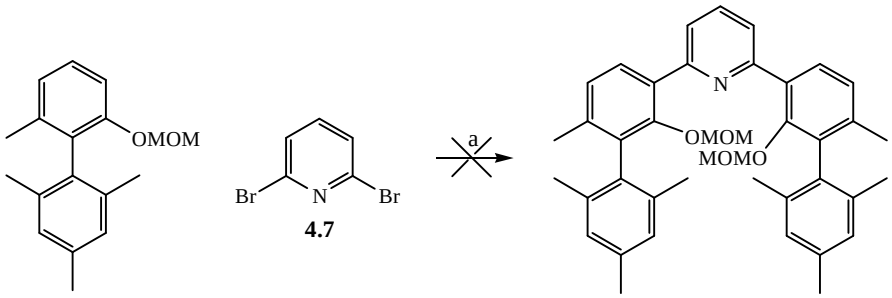
Thus, the synthesis of **4.60** was successfully carried out *via* pathway **A**, using the correct hydroxyl protecting group. However, as mentioned above, a promisingly shorter and more convergent pathway **B** have also been studied. This alternative synthesis will be detailed in the next section.

IV. 2. 5. Synthesis of the ligand core via organometallic cross-coupling

In parallel to the above described synthesis, several efforts have been made on the organometallic coupling between biphenyl **4.38** and 2,6-dibromopyridine **4.7**.

Initial tests were carried out under the well known Negishi cross-coupling conditions. The applied procedure begins with the *ortho*-lithiation of **4.38**, followed by transmetallation using zinc-chloride, and finally, the coupling of the organozinc species with 2,6-dibromopyridine in the presence of palladium catalyst (*Scheme 122*).

Unfortunately, no coupling product was detected. As demonstrated in earlier experiments, the *ortho*-lithiation of substrate **4.38** proceeds smoothly and efficiently. Thus, the failure of the reaction originates either from the transmetallation step or from the palladium coupling process.

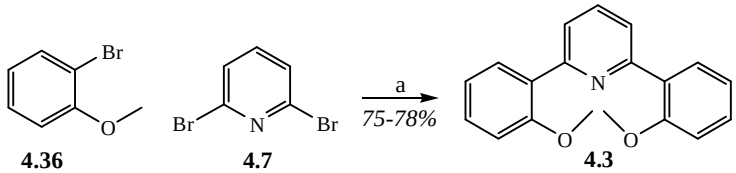


4.38 **4.7** **4.43**

a) i. BuLi, THF, -78°C to 0°C; ii. $ZnCl_2$, -78°C or 0°C; iii. 0.5 eq. **4.7**, $Pd(PPh_3)_4$, reflux.

Scheme 122

Later on, we found that the Corriu-Kumada cross-coupling reaction could be successfully applied to the formation of **4.3**.[138] The synthesis begins with the preparation of the Grignard reagent derived from the commercially available 2-bromo-anisole **4.36**. The subsequent coupling is carried out with 2,6-dibromo-pyridine in the presence of a nickel catalyst (*Scheme 123*). We obtained **4.3** in good yield by this remarkably short synthetic route.



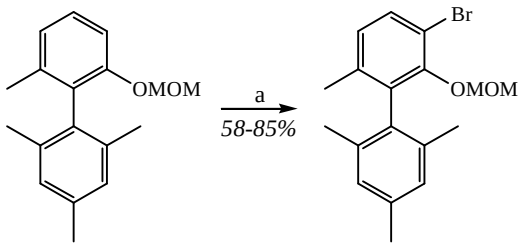
4.36 **4.7** **4.3**

a) i. Mg, THF, RT; ii. 0.5 eq. **4.7**, 3 mol% $NiCl_2$dppe, 0°C to RT, overnight.

Scheme 123

[138] a. Li Y.; Liu Y.; Bu W.; Guo J.; Wang Y. *Chem. Commun.* **2000**, 1551

To apply the same coupling to the synthesis of **4.43**, the corresponding brominated starting material has to be prepared. *Ortho*-lithiation of **4.38**, followed by the addition of bromine, provided **4.61** in good yield.

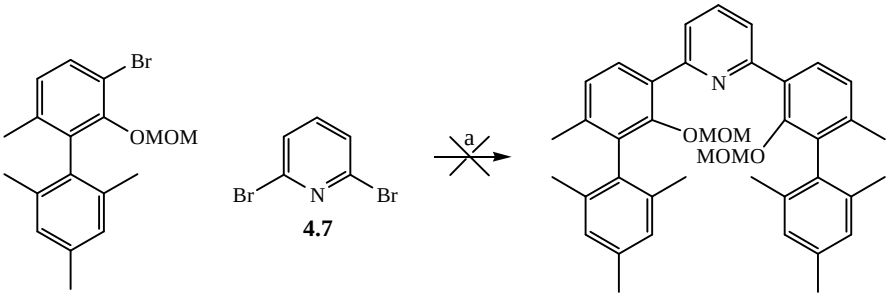


4.38 **4.61**

a) i. *n*-BuLi, THF, -78°C to RT; ii. Br_2 in hexane, -78°C to RT.

Scheme 124

However, **4.61** was not a suitable substrate for the coupling reaction (*Scheme 125*). Indeed, the corresponding Grignard reagent didn't form completely, even upon heating, and the coupling didn't work at all. Interestingly, about *60%* of the recovered starting material was debrominated, thus confirming the formation of some organomagnesium species.

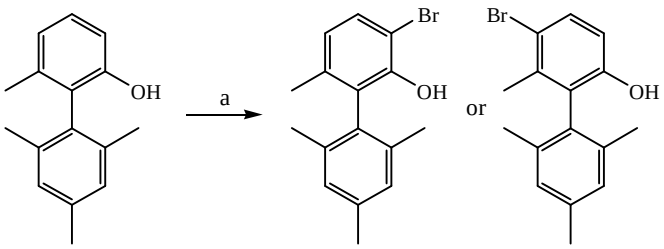


4.61 **4.7** **4.43**

a) i. Mg, THF, reflux; ii. 0.5 eq. **4.7**, 3 mol% $NiCl_2$dppe, 0°C to RT, overnight.

Scheme 125

Once again, we decided to change the protecting group of the hydroxyl function back to the original methoxy group. However, since we couldn't find appropriate conditions for the *ortho*-lithiation of **4.35**, another strategy was attempted to obtain **4.64**. The bromination of the hydroxy-biphenyl **4.20** was tested initially under different conditions (*Scheme 126* and *Table 7*). Using *N*-bromo-succinimide bromination occurred *para* to the hydroxyl functionality (*Entry 1*). However, low temperature bromination with *N*-bromo-dimethylamine or a mixture of *t*-butylamine and bromine provided exclusively the required regioisomer **4.62** (*Entry 2 and 3*). In the latter cases, the directed attack of the electrophile by the hydroxyl group explains the regioselectivity; the bromination probably occuring *via* a hypobromite intermediate.[139]



4.20 **4.62** **4.63**

a) See conditions in *Table 7*.

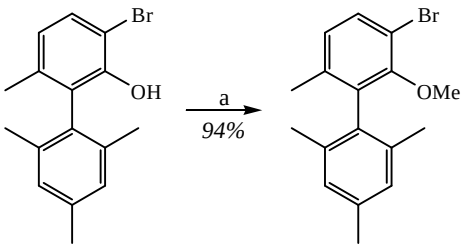
Scheme 126

Entry	Reagent	Conditions	*Yield*
1	*N*-bromo-succinimide	DMF, RT	*62%* **4.63**
2	Me_2NBr	Toluene, -15°C to RT	*38%* **4.62**
3	*t*-$BuNH_2$, Br_2	Toluene -78°C to RT	*54%* **4.62**

Table 7

[139] Pearson D. E.; Wysong R. D.; Breder C. V. *J. Org. Chem.* **1967**, *32(7)*, 2358

Continuing the synthesis, **4.62** was transformed to **4.64** *via* a common procedure in excellent yield (*Scheme 127*).

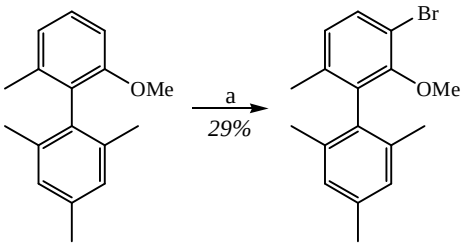


4.62 **4.64**

a) K_2CO_3, Me_2SO_4, acetone, reflux.

Scheme 127

In the meantime, we also found some conditions to accomplish the *ortho*-lithiation of **4.35** (*Scheme 128*). However, the yields remained low.

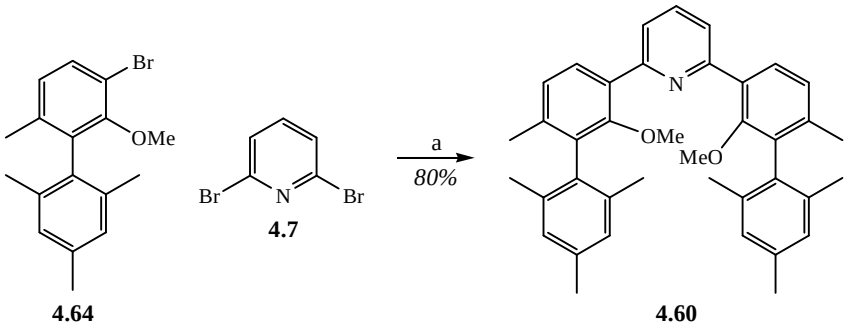


4.35 **4.64**

a) i. 2 eq. *n*-BuLi, 2 eq. TMEDA, ether (0.1M), 2h, RT;
ii. Br_2 in hexane, -78°C to RT.

Scheme 128

Having developed an easy access to **4.64**, we could carry out the key step of pathway **B** (*Scheme 129*). To our delight, the organomagnesium reagent formed smoothly at room temperature and **4.60** was obtained in an excellent yield.



4.64 **4.7** **4.60**

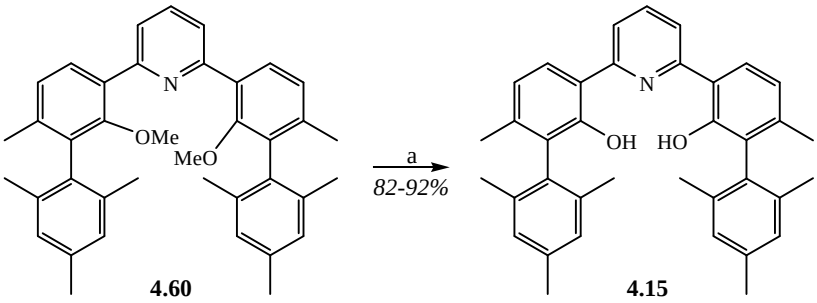
a) i. Mg, THF, RT; ii. 0.5 eq. **4.7**, 3 mol% $NiCl_2$dppe, 0°C to RT, overnight.

Scheme 129

Thus, both pathways **A** and **B** could be successfully applied for the synthesis of **4.60**, and the second method proved to be the most efficient one.

IV. 2. 6. Cleavage of the hydroxyl protecting groups

The last step of our ligand synthesis is the deprotection of the hydroxyl functionalities. Using molten pyridinium hydrochloride, ligand **4.15** was obtained in a remarkably high yield (*Scheme 130*).

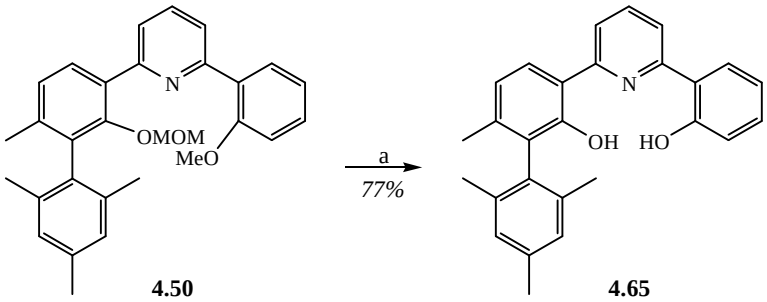


4.60 **4.15**

a) Pyridinium.HCl, 210°C, 2h.

Scheme 130

Recognizing the opportunity to assemble and test an asymmetrically substituted diaryloxy-pyridine ligand, the deprotection of **4.50** was carried out as well, using the same reagent (*Scheme 131*).

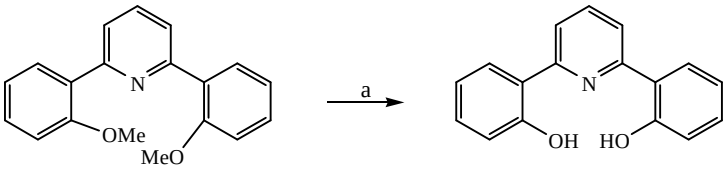


4.50 **4.65**

a) Pyridinium.HCl, 210°C, 2h.

Scheme 131

However, as mentioned before, being afraid of potential racemisation, we wanted to avoid these harsh conditions in the synthesis of the chiral, enantiopure ligands. Our attempts to use easily cleavable hydroxyl protecting group for the ligand synthesis failed. Thus, we decided to test other methods to cleave the methoxy groups (*Scheme 132* and *Table 8*). Several reagents have been tried until we found a successful and very efficient method.[140] Treating an ethanethiol solution of **4.3** with aluminium trichloride led to the smooth and quantitative deprotection of the hydroxyl functionalities in two hours at room temperature (*Entry 5*).



4.3 **3.16**

a) See conditions in *Table 8*.

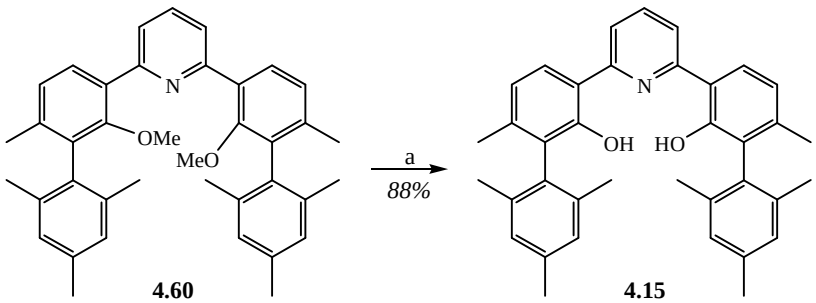
Scheme 132

[140] Node M.; Nishide K.; Fuji K.; Fujita E. *J. Org. Chem.* **1980**, *45*, 4275

Entry	Reagent	Temperature	*Results*
1	TMSI	RT	*recovered starting material*
2	BBr_3	RT	*boron complex*
3	HBr, Bu_4PBr	100°C	*monodeprotection*
4	HBr, AcOH	120°C	*monodeprotection*
5	EtSH, $AlCl_3$	RT	*complete conversion*

Table 8

The same conditions were successfully tested in the deprotection of **4.60** as well (*Scheme 133*).



4.60 **4.15**

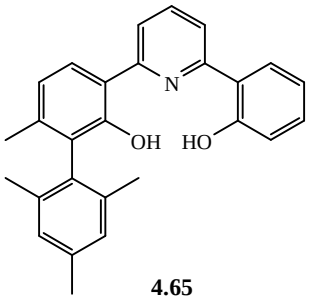
a) EtSH, $AlCl_3$, RT.

Scheme 133

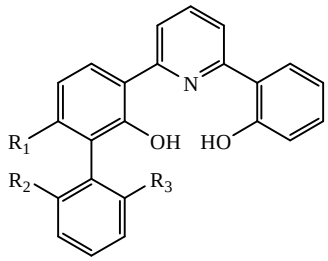
Having proved the feasibility of our synthetic approach, we could now start the construction of chiral derivatives. Meantime, recognizing the exciting potential of asymmetrically substituted diaryloxy-pyridines, we decided to turn our attention to the development of their synthesis.

IV. 3. Synthesis of the asymmetrically substituted diaryloxy-pyridine model

As we mentioned above, whilst investigating the synthesis of C_2 symmetric ligands, we prepared **4.65** and recognized its potential as a new type of ligand structure. It would be interesting to compare the chiral inducting effect of such asymmetrically substituted, chiral, enantiopure ligands and that of their C_2 symmetric counterparts.



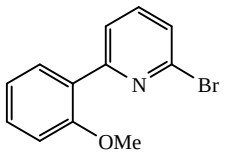
4.65



4.66

Scheme 134

We have already demonstrated that ligands possessing the general structure **4.66** can be assembled from the corresponding ketone and enaminone fragments. Alternatively, we decided to test their synthesis *via* subsequent organometallic couplings. As a part of this strategy, several efforts were made to prepare the fragment **4.67**.

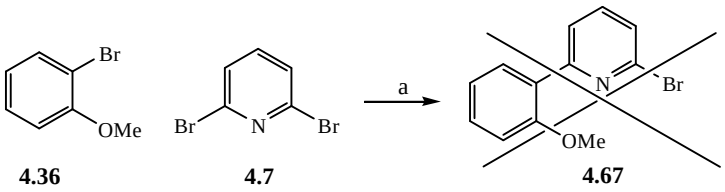


4.67

Scheme 135

Initially, we tested the previously successful Corriu-Kumada cross-coupling reaction by increasing the amount of the

dibromopyridine to one equivalent (*Scheme 136*). However, either the dibromopyridine reacted on both sides or it did not react at all.

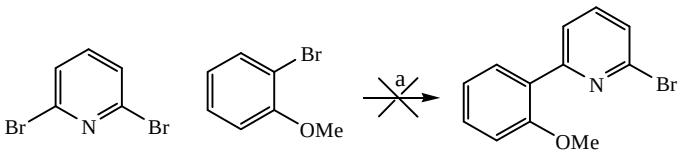


4.36 **4.7** **4.67**

a) i. Mg, THF, RT; ii. 1 eq. **4.7**, 3 mol% $NiCl_2$dppe, 0°C to RT, overnight.

Scheme 136

It has been published that one of the bromine of the 2,6-dibromopyridine can be selectively exchanged with *i*-PrMgCl.[141] However, applying this procedure in combination with the Corriu-Kumada cross-coupling did not lead to the desired adduct (*Scheme 137*). Sadly, the starting materials were mainly recovered and only traces of the monobromo-pyridine were formed.



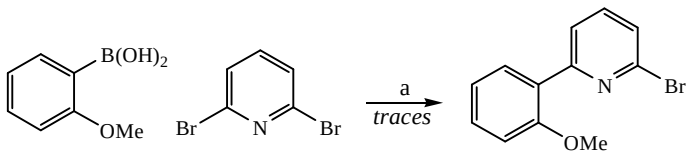
4.7 **4.36** **4.67**

a) i. *i*-PrMgCl, THF, RT; ii. **4.36**, 10 mol% $NiCl_2$dppe, 0°C to reflux, overnight.

Scheme 137

Next, we attempted to unit these fragments by a Suzuki cross-coupling under conditions that were found to be appropriate for a similar reaction as described by Chan.[142] Unfortunately, only traces of **4.67** could be obtained (*Scheme 138*).

[141] Trécourt F.; Breton G.; Bonnet V.; Mongin F.; Marsais F.; Quéguiner G. *Tetrahedron Lett.* **1999**, *40*, 4339
[142] Zhang H.; Tse M. K.; Chan K. S. *Synth. Commun.* **2001**, *31(8)*, 1129

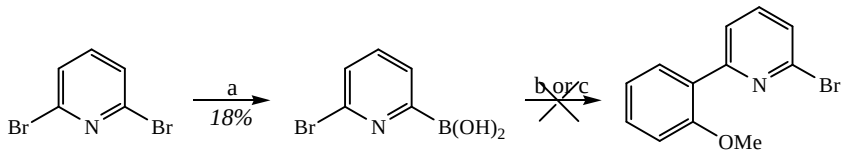


4.68 **4.7** **4.67**

a) *t*-BuOK, *t*-BuOH, 10 mol% $Pd(PPh_3)_4$, DME, 90°C.

Scheme 138

Later on, attracted by the publication of Rault *et al*., we converted the 2,6-dibromopyridine to 6-bromopyridin-2-yl-boronic acid **4.69**, and employed it under different coupling conditions (*Scheme 139*).[143] However, we could not prepare **4.67** by this approach either.



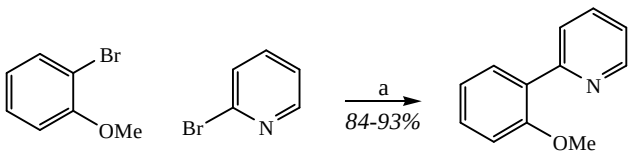
4.7 **4.69** **4.67**

a) i. *n*-BuLi, THF, -78°C; ii. $B(i\text{-}PrO)_3$, -78°C to RT; iii. $HCl_{(aq.)}$, 0°C; b) **4.36**, 4 mol% $Pd(PPh_3)_4$, Na_2CO_3, DME, reflux; c) **4.36**, 1 mol% Pd_2dba_3, 2 mol % X-Phos, K_3PO_4, toluene, reflux.

Scheme 139

At that point, it was decided to apply our operational Corriu-Kumada cross-coupling conditions to the synthesis of **4.71**, and then, prepare **4.67** *via* a regioselective deprotonation, followed by a subsequent bromination. As expected, **4.71** was generated in excellent yield (*Scheme 140*).

[143] Bouillon A.; Lancelot J-C.; Santos J. S. O.; Collot V.; Bovy P. R.; Rault S. *Tetrahedron* **2003**, *59*, 10043

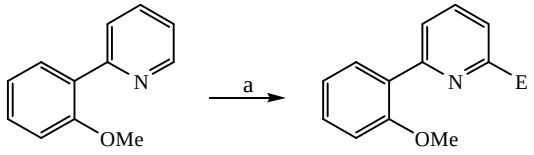


4.36 **4.70** **4.71**

a) i. Mg, THF, RT; ii. 1 eq. **4.70**, 3 mol% $NiCl_2$dppe, 0°C to RT, overnight.

Scheme 140

The regioselective deprotonation of **4.71** was described by Mongin *et al*. using lithium-tetramethylpiperidine (LiTMP).[144] Whilst we were able to reproduce their results using trimethylsilyl chloride as the electrophile, neither bromine, nor tetrabromomethane did afford the required product (*Scheme 141*).



4.71 **4.72**

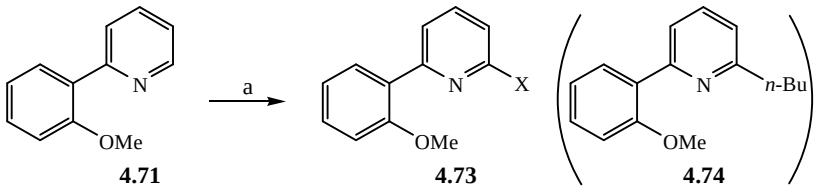
a) i. LiTMP, THF, -15°C; ii. electrophile.

Scheme 141

Next, we tried the deprotonation - halogenation procedure of Fort, described on the same substrate (*Scheme 142*).[145] According to their results, bases such as *n*-BuLi, *t*-BuLi, *n*-BuLi-TMEDA or BuLi-*t*-BuOK promote nucleophilic addition on the pyridine ring. Therefore, a less nucleophilic 'super base', formed from 2-dimethylaminoethanol (DMAE) and two equivalents of *n*-butyl lithium, was used for the regioselective deprotonation. Repeating their procedure and using hexachloroethane as the electrophile, we were able to obtain the desired halogenated product only in *18%* yield

[144] Rebstock A-S.; Mongin F.; Trécourt F.; Quéguiner G. *Org. Biomol. Chem.* **2003**, *1*, 3064
[145] Parmentier M.; Gros P.; Fort Y. *Tetrahedron* **2005**, *61*, 3261

instead of the described *82%* (*Entry 1*). The conversion of the starting material was complete. However, a large amount of butylated byproduct **4.74** was formed. Actually, this is not too surprising since the base was used in high excess. When the electrophile was added, the unreacted *n*-butyl-lithium was probably transformed rapidly into *n*-butyl-chloride which reacted further with our unquenched lithiated intermediate.



4.71 **4.73** **4.74**

a) i. LiDMAE - *n*-BuLi, toluene, -40°C; ii. electrophile, THF, -78°C.

Scheme 142

Entry	Electrophile	Addition	*Yield*
1	C_2Cl_6	dropwise	*18%*
2	C_2Cl_6	fast	*35%*
3	C_2Cl_6	inverted	*40%*
4	Br_2	dropwise	*<35%*
5	Br_2	fast, neat	*0%*
6	CBr_4	dropwise	*~10%*

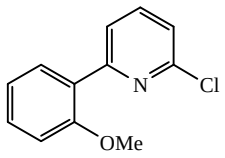
Table 9

At this point, we concluded that only the rate of addition of the electrophile might be different between the two protocols. Unfortunately, this data was not indicated in their procedure. Therefore, we modified the addition rate of the electrophile and we were delighted to note that a fast addition of the hexachloroethane doubled the yield of the halogenated product (*Entry 2*). Inverting the addition, that is, adding the reaction mixture to the solution of hexachloroethane resulted in a *40%* yield of **4.75** (*Entry 3*). It is

possible that a more concentrated solution of the electrophile, would lead to a further increase in the yield of the reaction.

Similar yield was obtained using only one equivalent of base and bromine as the electrophile (*Entry 4*). However, the conversion was not complete and the purification of the product was not successful. Interestingly, quenching the reaction by the fast addition of neat bromine did not give the brominated product at all; only the butylated byproduct was formed. Additionally, tetrabromomethane gave inferior results as compared to bromine.

In summary, a synthetically useful method for the preparation of **4.75** has been uncovered. This fragment can now be employed in the synthesis of asymmetrically substituted diaryloxypyridine ligands *via* metal-catalyzed C-C bond coupling reactions.



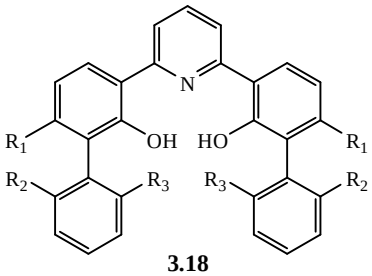
4.75

Scheme 143

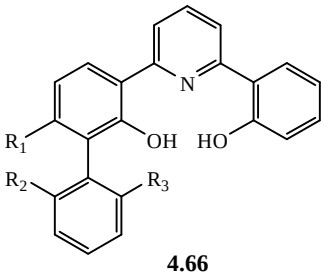
IV. 4. Conclusions

The model achiral ligands have been successfully prepared *via* two fundamentally different synthetic approaches. Besides the C_2 symmetric diaryloxy-pyridines, the construction of asymmetrically substituted, **4.66** type of ligands was also studied.

Having demonstrated the feasibility of our synthetic routes towards these ligands, we can now start the construction of chiral derivatives bearing the general structures shown in *Scheme 144*.



3.18



4.66

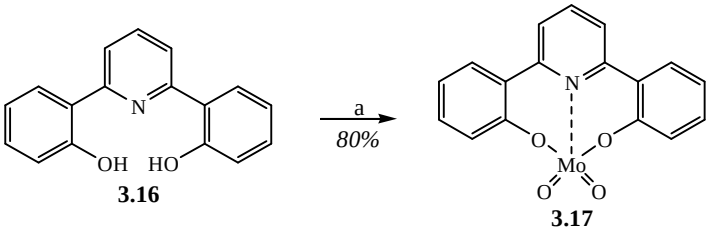
Scheme 144

Additionally, we envisage to prepare the corresponding molybdenum complexes of our model ligands and to test their activity in epoxidation and sulfoxidation reactions.

V. Complexes of achiral ligands and their reactivity

V. 1. Formation of complex 3.17

We prepared complex **3.17** in good yield from commercially available $MoO_2(acac)_2$ and ligand **3.16** by a simple ligand exchange reaction (*Scheme 145*). The formed orange complex can be separated easily from the reaction mixture by filtration. If necessary, it can be purified from $MoO_2(acac)_2$ impurities by shortly refluxing the mixture in dichloromethane, followed by precipitation of the partially dissolved complex with pentane and filtration.



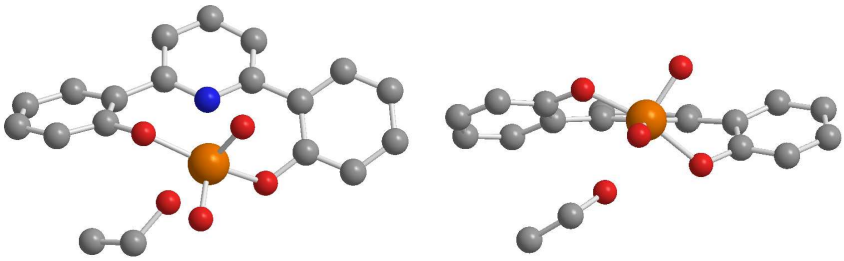
3.16 **3.17**

a) $MoO_2(acac)_2$, DCM, RT, 24h.

Scheme 145

The isolated complex was analyzed by NMR and IR spectroscopy as well as Mass Spectrometry. More importantly, its structure was unambiguously determined by single crystal X-Ray diffraction analysis. The crystallization was carried out in a dichloromethane solution exposed to an ethanol atmosphere, at -20°C. Based upon the results of the X-Ray analysis, complex **3.17** is mononuclear. It contains the *cis*-MoO_2 structural unit of the parent complex and ligand **3.16** being coordinated as expected by its three donor atoms. The complex **3.17** has a slightly distorted tetragonal bipyramidal geometry in which the sixth coordination site of the molybdenum is occupied by an ethanol substituent. Taking as the

main axis the line determined by the nitrogen of the pyridine, the molybdenum centre and one of its oxo-group, the square plane of the bipyramidal structure is constituted by the phenolic oxygen atoms placed in diagonal positions, the second oxo group and the oxygen of a coordinated ethanol molecule. [146]



*X-Ray structure of complex **3.17** from different views*

It has to be pointed out, that one of the phenolic oxygens is positioned above and the other one is positioned below the plane of the pyridine ring. This important structural feature suggests that complex **3.17** has two enantiomeric forms. If these enantiomeric forms are stable, or if they can be easily converted into each other, remains to be determined. Obviously, such an inter-conversion can be detrimental in the case of asymmetric catalysis, since the enantiomers might lead to opposite facial selectivity. However, we expected that, by preparing the catalyst from a chiral enantiopure ligand, one of the diastereoisomeric forms will be thermodynamically favoured.

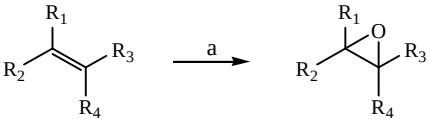
As mentioned above, the sixth coordination place of the molybdenum is occupied in the crystalline complex by a coordinating ethanol which originates from the crystallization solvent. An interesting observation, made during the preparation of this complex

[146] For selected bond lengths and angles see the experimental part.

in different solvents, suggests us that the sixth coordinated ligand occupies a labile position. Indeed, carrying out the ligand exchange reaction in dichloromethane produces a complex which has an orange colour. On the other hand, the complex, prepared in methanol, displays a light lemon yellow taint, which turns to orange by drying it on the vacuum pump. Additionally, dissolving the orange complex in methanol or dimethyl sulfoxide gives an orange solution which turns slowly to light lemon yellow, the same colour as that of the crystalline complex. Such colour changes might be the sign of a change in the complex geometry and/or in the number of coordinated ligands. However, we do not have yet clear-cut evidence for the existence of the penta-coordinated form, since we could not crystallize the complex without the use of a coordinating solvent. Accordingly, the formation of polymeric solid state structure cannot be excluded.

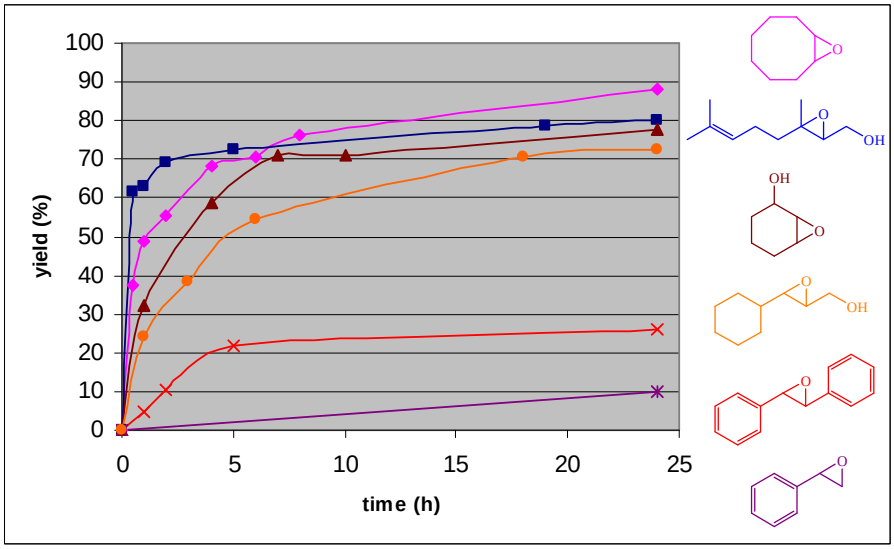
V. 2. Initial reactivity tests of complex 3.17

Having succeeded in the synthesis of complex **3.17**, we could test its activity as an oxidation catalyst. Differently substituted alkenes and some allylic alcohols were chosen as substrates and reacted with 0.5 mol% of the catalyst in the presence of *t*-butyl-hydroperoxide as the stoichiometric oxidizing agent (*Scheme 146*).



5.1 **5.2**

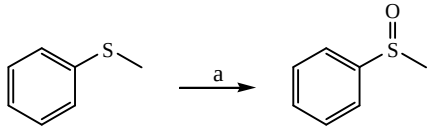
a) 0.5 mol% catalyst **3.17**, 1 eq. *t*-BuOOH, DCM, 50°C.



Scheme 146

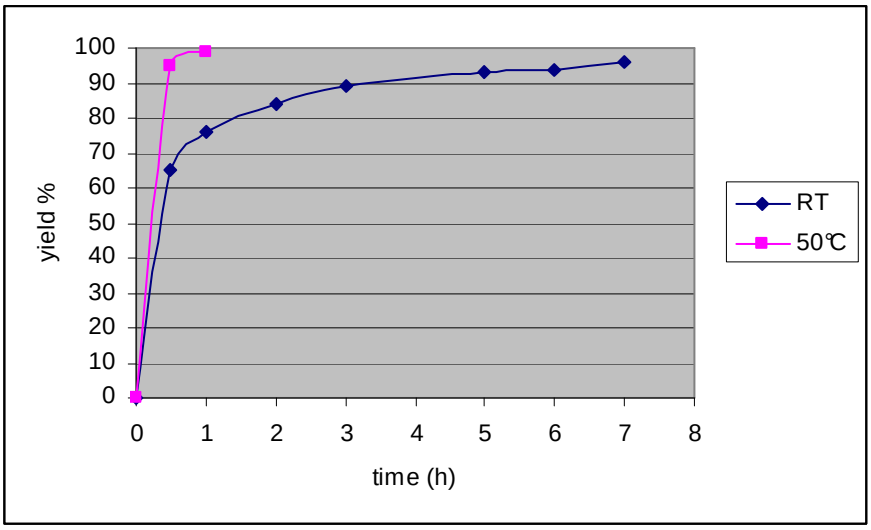
As can be seen, the oxidation of electron rich alkenes and allylic alcohols proceeded smoothly, leading to the corresponding epoxides in high yields. On the other hand, the oxidation of *trans*-stilbene and of styrene was much slower under these conditions. As expected with metal-catalysis, geraniol was regioselectively epoxidized next to its hydroxyl function; the other isomer was only formed in trace amounts.

Interestingly, the catalyst displayed even higher activity in sulfoxidation reactions. The oxidation of thioanisole was essentially complete within 30 minutes at 50°C, and only slightly slower at room temperature (*Scheme 147*).



5.3 **2.14**

a) 1 mol% catalyst **3.17**, 1 eq. *t*-BuOOH, DCM.

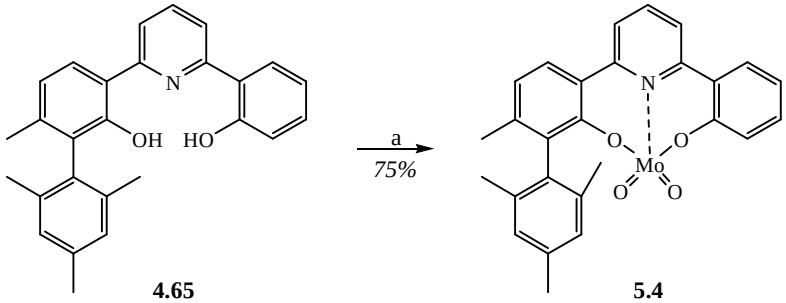


Scheme 147

Importantly, complex **3.17** could be recovered at the end of the reaction, proving the oxidative stability of the ligand. Additionally, a blank test was carried out by replacing complex **3.17** with ligand **3.16**. No metal was present in this reaction. After two hours, the formation of about *1%* sulfoxide was detected, and ligand **3.16** was recovered unchanged. Furthermore, a similar conversion has been achieved by carrying out the reaction without any ligand at all.

V. 3. Formation of complex 5.4 and 5.5

Complex **5.4** was easily formed by employing the corresponding ligand exchange reaction (*Scheme 148*).

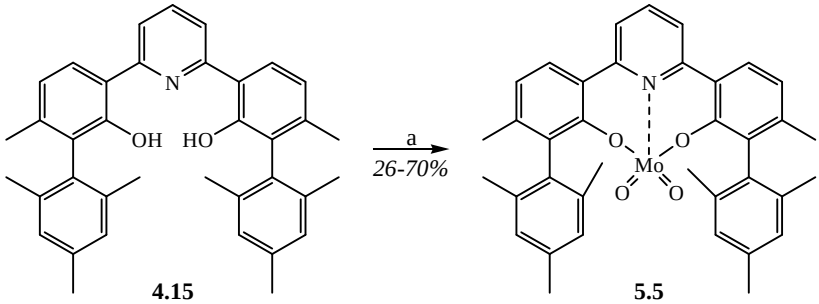


4.65 **5.4**

a) $MoO_2(acac)_2$, DCM, RT, 24h.

Scheme 148

On the other hand, to prepare complex **5.5** in a similarly high yield, the temperature had to be raised up a little (*Scheme 149*). The isolation and purification procedures for complexes **5.4** and **5.5** were the same as for species **3.17**.



4.15 **5.5**

a) $MoO_2(acac)_2$, see conditions in *Table 10*.

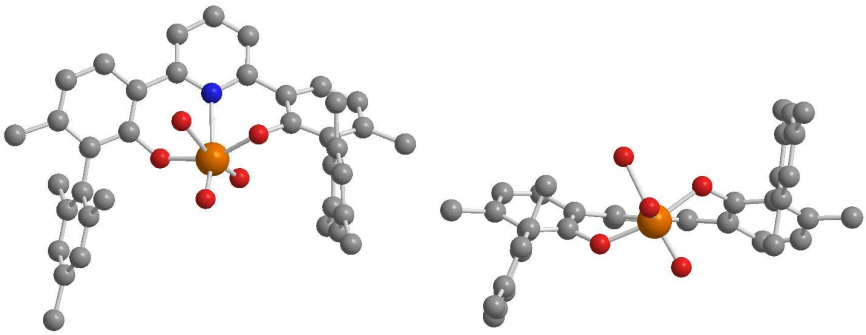
Scheme 149

Entry	Conditions	*Yield*
1	DCM, RT, 48h	*26-30%*
2	DCE, 50°C, 24h	*70%*

Table 10

Again, these new organometallic compounds were obtained as orange solids that dissolved slowly in coordinating solvents, leading to lemon yellow solutions.

Both complexes were analyzed by NMR and IR spectroscopy as well as Mass Spectrometry. Furthermore, single crystal X-Ray diffraction analysis of complex **5.5** could be successfully carried out. The structure of this complex corresponded very well to that of the molybdenum derivative **3.17**. In this case, we found a water molecule coordinated at the sixth position.[147] As additional structural feature, we can observe the perpendicular arrangements of the phenyl rings, forming small walls around the metal centre.

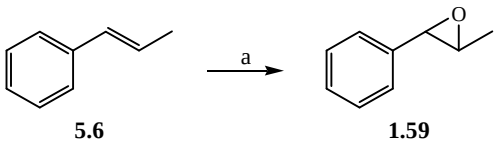


*X-Ray structure of complex **5.5** from different views*

[147] For selected bond lengths and angles see the experimental part.

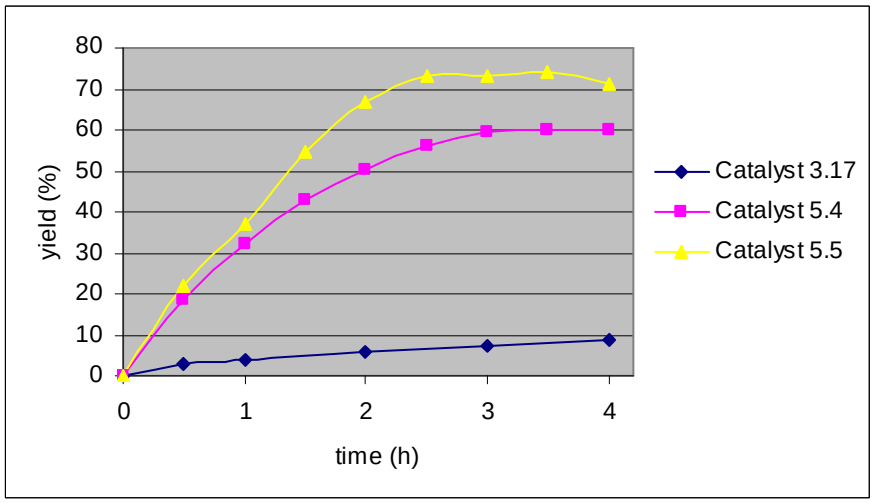
V. 4. Comparison of the three complexes in terms of reactivity

With the three complexes in hand, we became interested in comparing their relative reactivity in epoxidation and sulfoxidation reactions. For this purpose, the epoxidation of *trans*-β-methyl styrene was selected as the test reaction. To obtain reasonable conversions, 1 mol% of catalyst and two equivalents of *t*-butyl-hydroperoxide were used (*Scheme 150*).



5.6 **1.59**

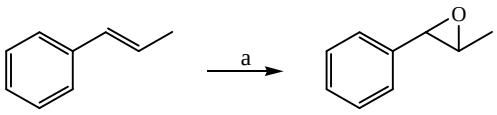
a) 1 mol% catalyst, 2 eq. *t*-BuOOH, DCM, reflux



Scheme 150

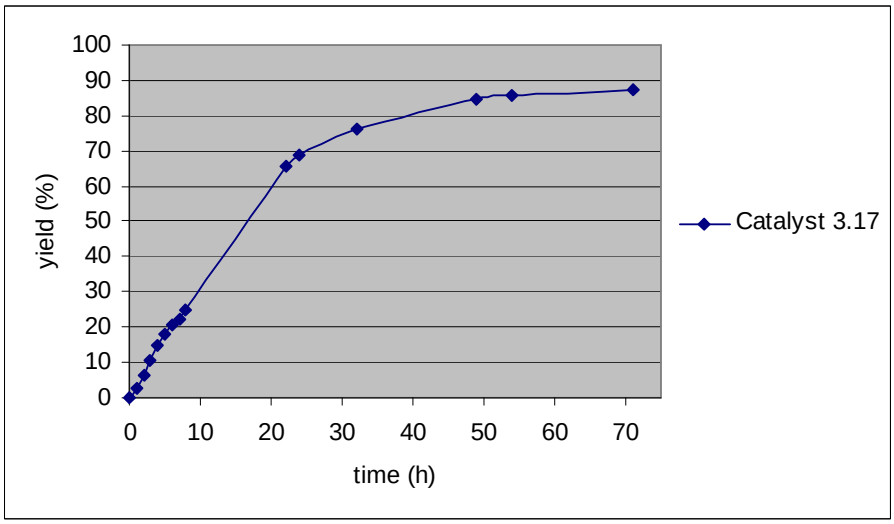
As can be seen from *Scheme 150*, catalyst **5.4** and **5.5** proved to be much more reactive towards this substrate than complex **3.17**. Moreover, the biggest catalyst **5.5** displayed the highest reactivity. Unfortunately, after a few hours of reaction, the degradation of the sensitive epoxide took place. Later on, we found that the degradation

of the epoxide could be completely avoided by carefully controlling the reaction temperature and by minimizing the evaporation of the solvent during the prolonged reaction time. With these precautions, high yield of the epoxide could be achieved using catalyst **3.17**, though in a relatively long reaction time (*Scheme 151*).



5.6 **1.59**

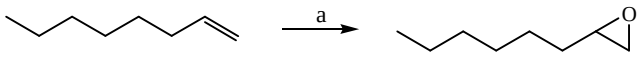
a) 1 mol% catalyst, 2 eq. *t*-BuOOH, DCM, 40°C.



Scheme 151

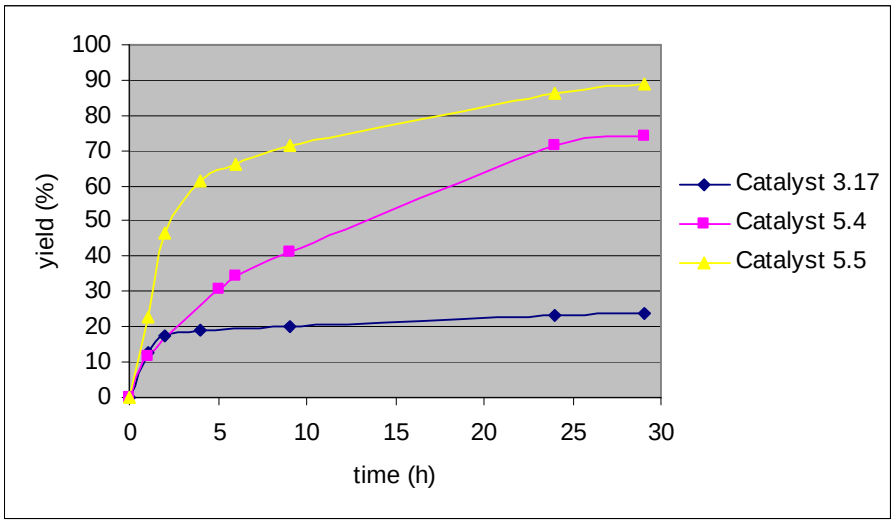
The structure-reactivity relationship of the complexes was confirmed by the results obtained during the epoxidation of 1-octene (*Scheme 152*). Since complex **3.17** gave only traces of the corresponding epoxide after a few hours of reaction at 40°C, the temperature was increased to 60°C for the comparative study. For obvious reasons, the solvent was changed to dichloroethane. Under

these new conditions, the degradation of the epoxide was not observed at all.



5.7 **5.8**

a) 1 mol% catalyst, 2 eq. *t*-BuOOH, DCE, 60°C.

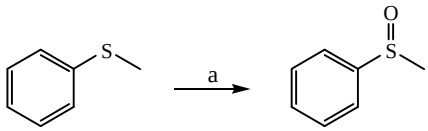


Scheme 152

The relationship between the size of the ligand and the reactivity of the catalysts is a remarkable feature of these epoxidations. On the other hand, such differences were not observed in the sulfoxidation reactions due to the high activity of all three catalysts toward those substrates. These reactions were carried out at room temperature, in the presence of only one equivalent of *t*-butyl-hydroperoxide to avoid any overoxidation.

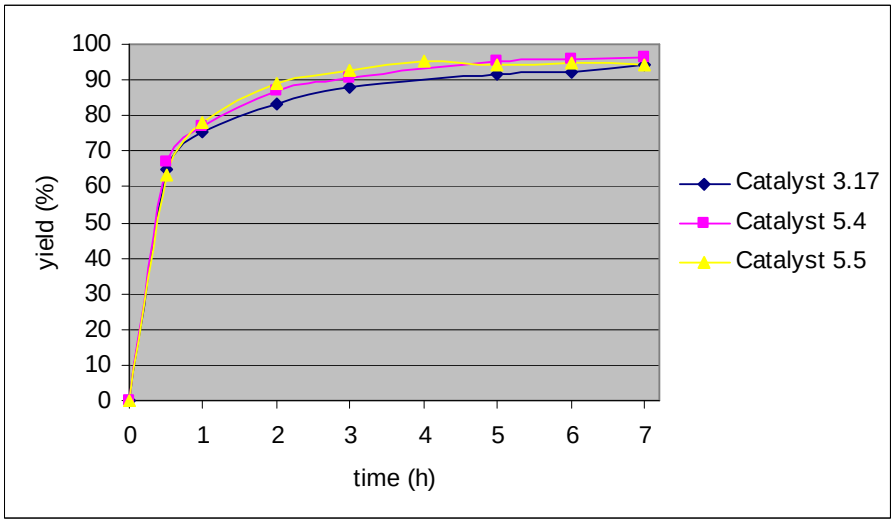
Under these conditions, the oxidation of thioanisole was particularly fast at the beginning of the reaction; the conversion reaching already *60%* in less than 30 minutes. Afterwards, it slowed

down and gave the usual saturation curve (*Scheme 153*). Only traces of sulphone, if any, were observed.



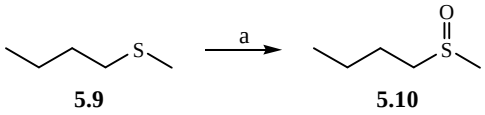
5.3 **2.14**

a) 1 mol% catalyst, 1 eq. *t*-BuOOH, DCM, RT.



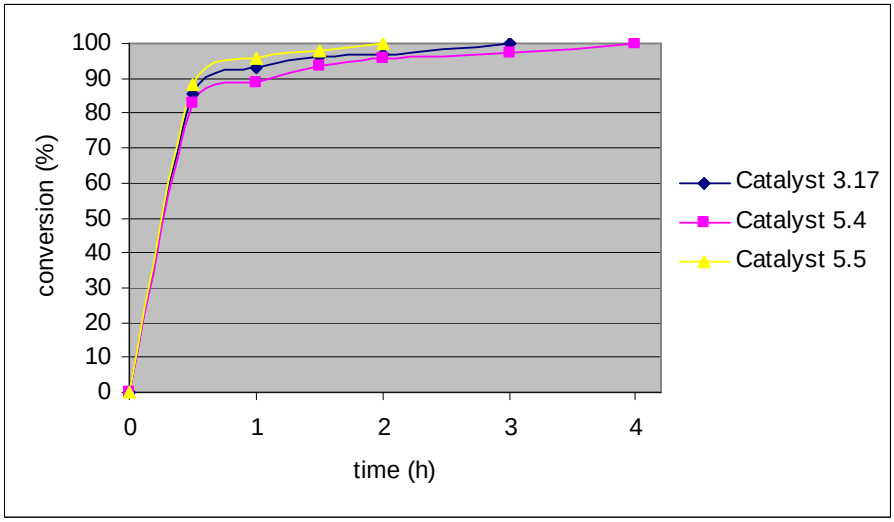
Scheme 153

The oxidation of the more electron rich *n*-butyl-methyl-sulphide was even faster (*Scheme 154*). The conversion went already above *80%* after 30 minutes. Here again, the corresponding sulphone was detected only in traces.



5.9 **5.10**

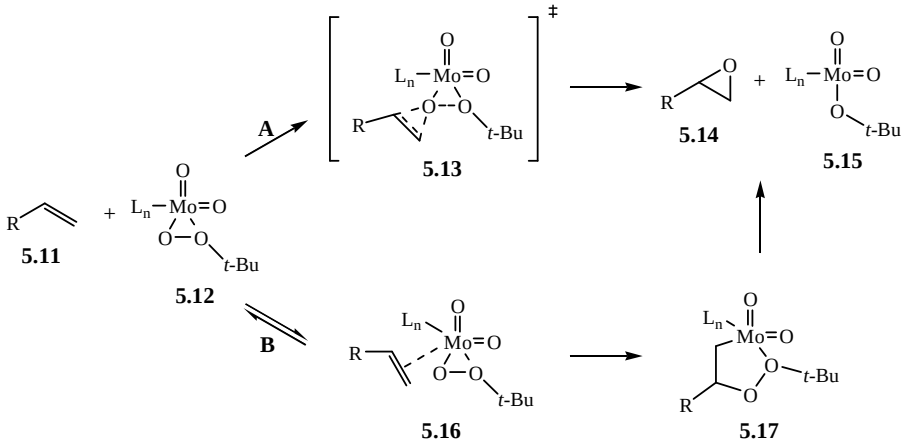
a) 1 mol% catalyst, 1 eq. *t*-BuOOH, DCM, RT.



Scheme 154

V. 5. Mechanistic discussions

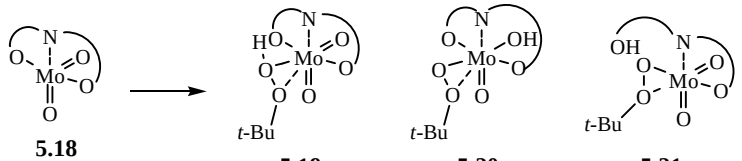
Concerning the mechanism of the Mo(VI)-catalyzed epoxidation of olefins with alkyl hydroperoxides, the formation of a Mo(VI) alkyl peroxide intermediate and the transfer of the distal oxygen atom of the alkyl peroxide rather than of an oxo ligand are generally agreed upon. However, whether the reaction proceeds by direct oxygen atom transfer in a concerted single-step process (**A**) or *via* the formation of a Mo(VI)-olefin complex and a peroxymetallacycle intermediate (**B**) remains a subject of debate (*Scheme 155*).



Scheme 155

Detailed kinetic and mechanistic studies have not yet been carried out with our molybdenum catalysts. However, the interesting structure-activity relationship of these three catalysts, observed in the oxidation of the less reactive alkenes, raises some questions.

Is it possible that the oxidation is carried out by the coordinated alkyl hydroperoxide (species **5.19**), or is the formation of a Mo(VI) alkyl peroxide intermediate mandatory? Regarding the coordination pattern of our molybdenum catalysts, the formation of a Mo(VI) alkyl peroxide intermediate would require, either the transformation of an oxo-group (species **5.20**), or the partial dissociation of our three dentate ligand (species **5.21**). Although we find the first two possibilities more likely, we cannot exclude the partial de-coordination of our tridentate ligands during the oxidation process.



Scheme 156

It is possible that the observed relative reactivity of our complexes derives from the fact that the bigger the aromatic cavity, the easier the approach of the olefin to the molybdenum centre because of the increasing potential for π-π interactions.

On the other hand, the partial dissociation of our tridentate ligands during the oxidation process could also explain the observed structure-activity relationships. As we know, increasing the steric bulk of the ligand requires either longer reaction times and/or slightly elevated temperatures for the complex preparation. Accordingly, we can imagine that the de-coordination of one or more donor atoms of the pyridine ligands occurs easier in the same order. Thus, when using a bulkier catalyst, the concentration of active catalytic species, in which the pyridine ligand is partially detached, would be higher, leading to the increased rate of oxidation.

Obviously, the partial dissociation of the enantiopure pyridine ligands can be detrimental to the enantioselectivity of the oxidations. Therefore, it is to be avoided.

V. 6. Conclusions

We have successfully prepared, isolated and characterized complexes **3.17**, **5.4** and **5.5**. The exact structures of two of them were determined by single crystal X-Ray diffraction analysis. All three

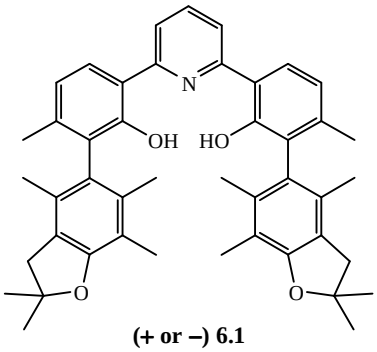
molybdenum catalysts proved to be very active in the oxidation of electron rich olefins and sulphides. In the case of less reactive substrates, an interesting structure-reactivity relationship has been revealed, in which the greater the steric bulk of the pyridine ligand, the higher the activity of the catalyst. Based upon these studies, remarkable results can be achieved even for less electron rich substrates, such as styrene derivatives and terminal alkenes.

VI. Chiral ligands and their complexes

VI. 1. Complex 6.8

VI. 1. 1. Synthesis of ligand 6.1

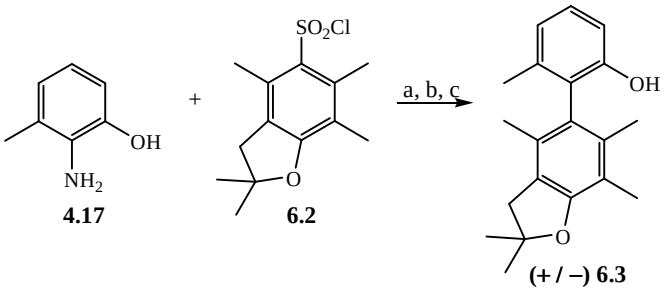
Having confirmed the feasibility of our synthetic route towards complex disubstituted pyridine ligands, and having shown that their derived molybdenum complexes were competent catalysts in olefin epoxidation and sulphur oxidation, we began the synthesis of the chiral ligands. At the onset, rather than an enantioselective preparation, it was planned to separate the enantiomers of the hydroxy-biphenyl intermediates, and build up the ligands from enantiopure biphenyl fragments. Ligand **6.1** was chosen as the first chiral target due to the commercial availability of the required starting materials (*Scheme 157*).



(+ or –) 6.1

Scheme 157

Hydroxy-biphenyl intermediate **6.3** was prepared, in a manner analogous to the model substrate, by the three steps procedure of Motherwell, in a good overall yield (*Scheme 158*). We were able to separate the enantiomers of **6.3** by chiral, analytical HPLC. However, these conditions were not suitable for preparative scale separation.

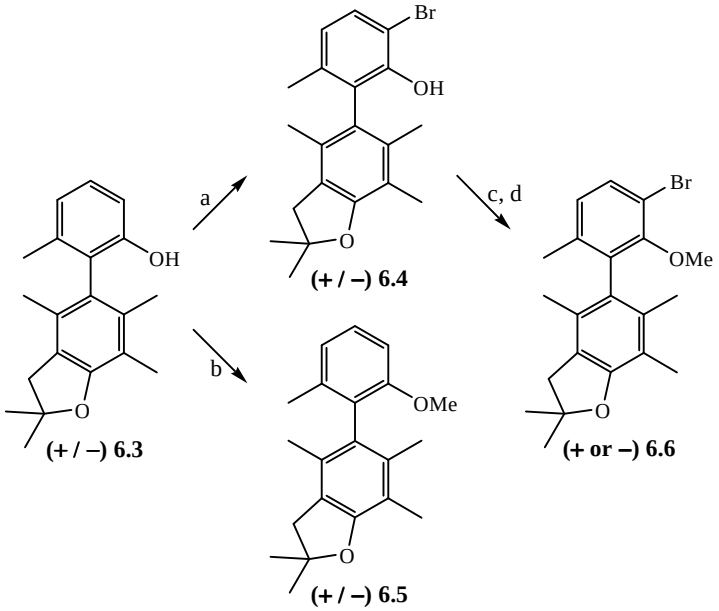


a) Et_3N, DCM, 0°C to RT; b) HBF_4, *i*-$C_5H_{11}ONO$, EtOH, 0°C;
c) $TiCl_3$, $HCl_{(aq)}$, acetone, 0°C, 48-62% over the three steps.

Scheme 158

Based upon our previous experience, we could continue the synthesis according to two different pathways. The required bromide function could be introduced either by low temperature bromination of phenol **6.3** or by following the established *ortho*-bromination protocol for the methoxy-biphenyl **6.5**. In fact, both **6.4** and **6.5** were prepared in small amount to verify if their enantiomers could be easily separated (*Scheme 159*). Fortunately, rather good HPLC conditions were found in the case of **6.4**, and its synthesis was reproduced on larger scale. Due to unforeseen technical problems, the enantiomers were separated by MPLC on a chiral semi-preparative AD column.

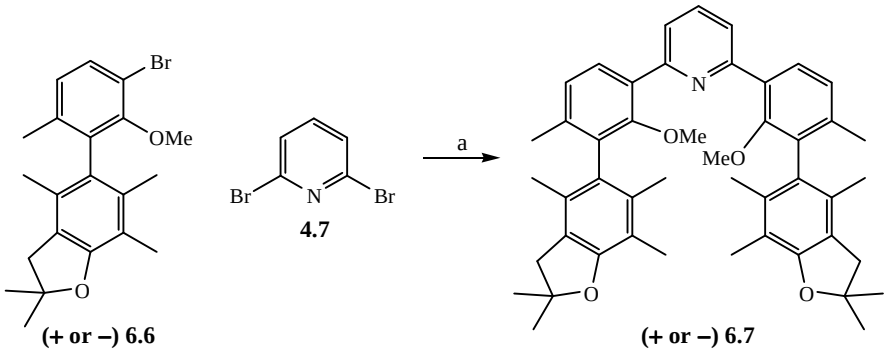
Having successfully obtained both enantiomers of **6.4**, we continued our synthesis with these enantiopure biphenyl fragments. Both enantiomers of **6.4** were transformed into their methoxy derivative **6.6** in good yield.



a) *t*-$BuNH_2$, Br_2, toluene, -78° to RT, 63-73%; b) NaH, MeI, THF, RT, 94%;
c) MPLC on chiral AD column; d) NaH, MeI, THF, RT, 82-87%.

Scheme 159

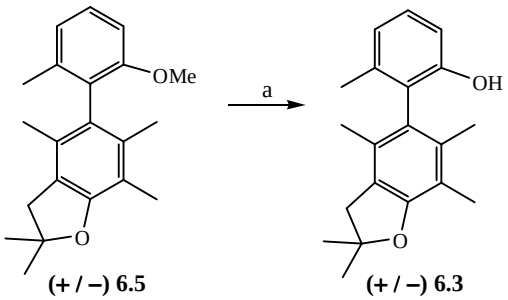
The Grignard reagents, derived from **6.6** required heating to be formed, and the nickel-catalysed coupling was successfully achieved for both enantiomers (*Scheme 160*).



a) i. Mg, THF, 60°C; ii. 0.5 eq. **4.7**, 3 mol% $NiCl_2$dppe, 0°C to RT, overnight, 48-66%.

Scheme 160

As mentioned earlier, the cleavage of the hydroxyl-protecting groups could be efficiently performed at room temperature. However, in the case of **6.7**, the methoxy groups are not the only ether functionalities present in the molecule, and some competitive, undesired side-reactions could be expected. To fine-tune the conditions, we tested **6.5** as a model substrate (*Scheme 161*).



(+ / –) 6.5 **(+ / –) 6.3**

a) See conditions in *Table 11*.

Scheme 161

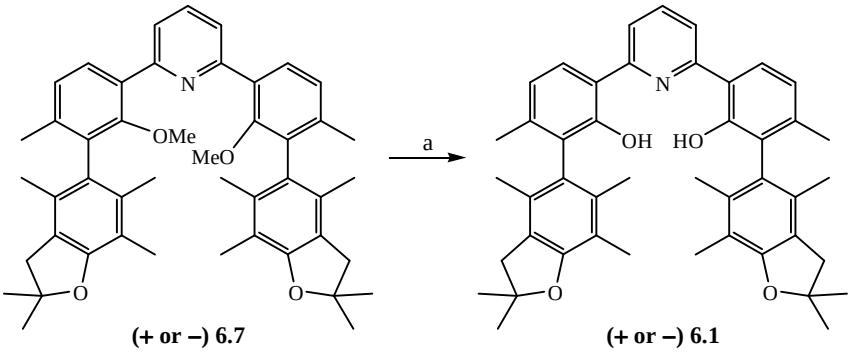
Entry	Conditions	*Results*
1	EtSH, $AlCl_3$, 0°C to RT, 2h	*complete conversion, ring opened byproduct*
2	EtSH, $AlCl_3$, 0°C to RT, 2h + DCM co-solvent	*75% clean conversion*

Table 11

Using the original procedure complete conversion was achieved, but some ring-opened byproduct formed as well (*Entry 1*). However, decreasing a little the amount of aluminium trichloride, and adding dichloromethane as a co-solvent, resulted in a slower and more selective transformation. Under these conditions, *75%* conversion was achieved in two hours, without the formation of any byproduct.

Applying this fine-tuned procedure to the deprotection of both enantiomers of **6.7** provided us with the corresponding ligands in good

yield (*Scheme 162*). We have to mention, however, that upon repeating this procedure, a small amount of ring-opened product can sometimes be formed.

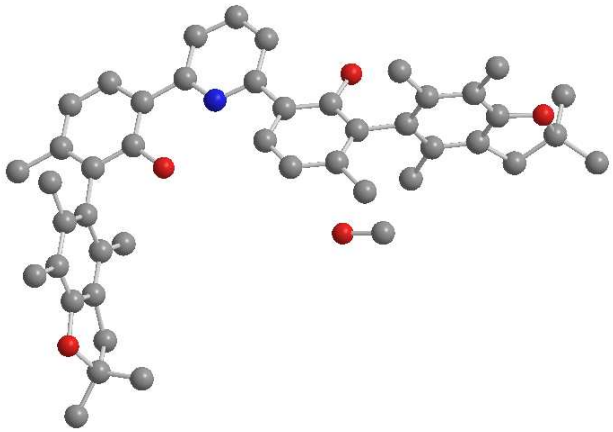


(+ or –) 6.7 **(+ or –) 6.1**

a) EtSH, $AlCl_3$, DCM, 0°C to RT, 2h, 55-65%.

Scheme 162

At the end of the synthesis, chiral HPLC analysis and optical rotation measurements of the ligand (+) and (-)-**6.1** confirmed their enantiopurities and enantiomeric relationship. Additionally, the single crystal X-Ray diffraction analysis of ligand (-)-**6.1** confirmed unambiguously the expected structure.[148]



*X-Ray structure of ligand (-)-**6.1***

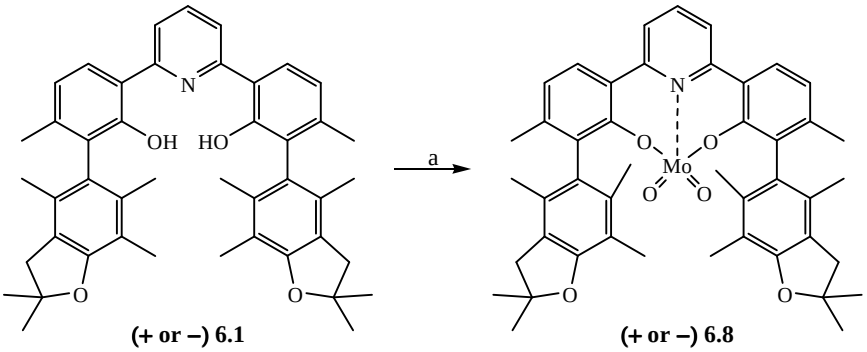
[148] For the analytical data see the experimental part.

It is interesting to note that the two biphenyl fragments are orientated differently in this crystal structure. One of them is fixed by a hydrogen-bonding between the phenol function and the nitrogen atom of the pyridine ring. The other one is twisted outward from the rest of the molecule. Fascinatingly, upon complexation, the strong coordinating ability of the molybdenum will be able to turn both biphenyl fragments toward the metal centre and fix them in that position.

VI. 1. 2. Complexation and X-ray

We described previously that the molybdenum complexes of the achiral ligands have helical chirality. However, we didn't have any evidence about the stability of these enantiomeric forms. Additionally, we suggested that preparing the catalyst from a chiral, enantiopure ligand, one of the diastereoisomeric forms will be thermodynamically favoured.

Both enantiomers of ligand **6.1** were reacted with $MoO_2(acac)_2$ to form the corresponding complexes (*Scheme 163*). These organometallic species had much higher solubility as compared to the previous ones. Therefore, we couldn't apply the same isolation and purification procedure. We prepared complex **6.8** by using an excess of the ligand to ensure the complete conversion of $MoO_2(acac)_2$. Then, the molybdenum catalyst was isolated by the evaporation of the solvent. It was further purified from the free acetylacetone and the excess of ligand **6.1** by a pentane wash. If the isolated complex still contained some $MoO_2(acac)_2$, a dichloromethane solution of **6.1** was added to it, and the process was repeated as often as necessary.



(+ or –) 6.1 **(+ or –) 6.8**

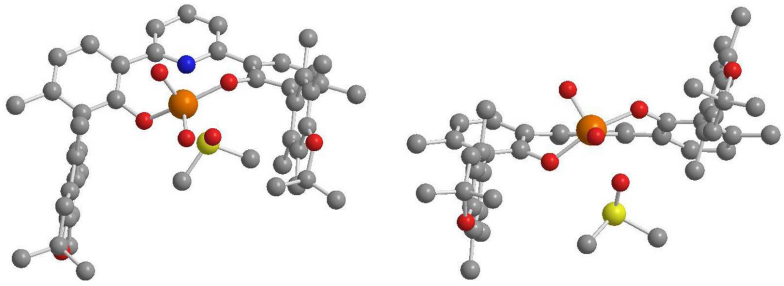
a) $MoO_2(acac)_2$, DCM, RT.

Scheme 163

Both complexes were analyzed by standard spectroscopic techniques. The ^{1}H and ^{13}C-NMR spectra did not reveal the existence of different diastereomeric forms. It suggested that the formation of the complex was completely diastereoselective, and that the catalysts, originating from the ligand (+) and (-)-**6.1**, were enantiomers to each other. A more unlikely hypothesis was that the NMR signals of the two diastereomeric forms overlapped with each others. Low temperature NMR spectroscopy was carried out to split these signals without success. Additionally, monitoring the coordination of (*S*)-1-phenyl-ethanol, a chiral enantiopure alcohol, to complex (+)-**6.8** by NMR spectroscopy, didn't reveal any sign of the presence of two diastereomeric forms.

Successful crystallization of the (+)-enantiomer allowed us to confirm the complex structure by X-Ray analysis. Crystals suitable for the analysis were obtained from a dimethyl sulfoxide solution and, consequently, we found a coordinating dimethyl sulfoxide molecule at the sixth coordination place around the molybdenum. Otherwise, very similar structural features and complex geometry were found as in

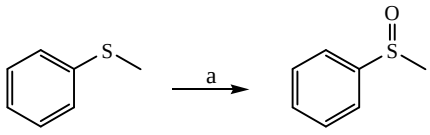
previous complexes.[149] The presence of the molybdenum atom let us to determine the absolute configuration of the biphenyl fragments of (+) and (-)-**6.1** ligand from this X-ray structure. Thus, the biphenyl fragments owning (+) optical rotation proved to have *S*, and those owning (-) optical rotation proved to have *R* absolute configuration.



*X-Ray structure of complex δ-(+)-(S,S)-**6.8** from different views*

VI. 1. 3. Oxidation tests

Having been able to prepare the chiral catalysts, the first oxidation tests were carried out on thioanisole (*Scheme 164* and *Table 12*). As in the previous experiments, 1 mol% of catalyst and one equivalent of *t*-butyl-hydroperoxide were employed.



5.3 **2.14**

a) 1 mol% catalyst (+ or −)-**6.8**, 1 eq. *t*-BuOOH.

Scheme 164

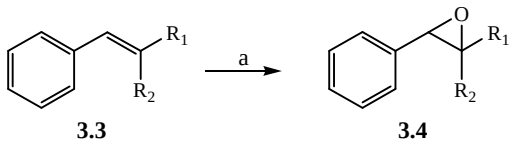
[149] For selected bond lengths and angles see the experimental part.

Entry	Solvent	Temperature	Reaction time	*Conversion*	*ee*
1	DCM	RT	3h	*98%*	*0%*
2	DCM	0°C	8h	*80%*	*0%*
3	PhMe	0°C	7h	*83%*	*0%*
4	EtOH	0°C	7h	*91%*	*0%*
5	MeCN	0°C	7h	*>40%*	*5%*
6	MeCN	-20°C	23h	*75%*	*0%*
7	DCM	-20°C	24h	*57%*	*0%*

Table 12

It is noteworthy that catalyst **6.8** oxidized thioanisole, at room temperature, even faster than catalyst **5.5**. Unfortunately, our chiral, enantiopure catalysts did not induce any enantioselectivity in the reaction. The high activity allowed us to decrease the reaction temperature, and different solvents were tested at 0°C. In a single case, a very low enantioselectivity was observed using acetonitrile as the solvent (*Entry 5)*. However, decreasing further the reaction temperature to -20°C did not result in any improvement in the enantioselectivity of the reaction, neither in acetonitrile nor in dichloromethane. These results are interesting since the previously obtained *5%* enantioselectivity is too high to be considered as an experimental mistake.

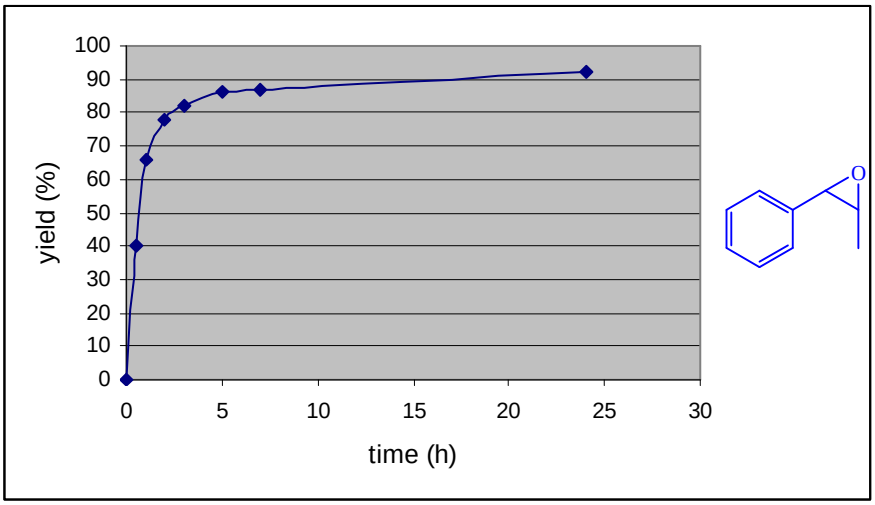
Using the chiral, (+) or (-)-**6.8** complex in the epoxidation of cinnamyl alcohol and *cis*- or *trans-β*-methyl-styrene did not lead to any asymmetric induction (*Scheme 165*). Remarkably, the epoxidation of *cis-β*-methyl-styrene was completely stereospecific, giving exclusively the *cis* epoxide.



3.3 **3.4**

a) 1 mol% catalyst (+ or −)-**6.8**, 2 eq. *t*-BuOOH, DCE, 40°C

Entry	Substrate	Reaction time	*Yield*	*ee*
1	*trans-β*-methyl-styrene	5h	*29%*	*0%*
2	cinnamyl-alcohol	7h	*35%*	*0%*



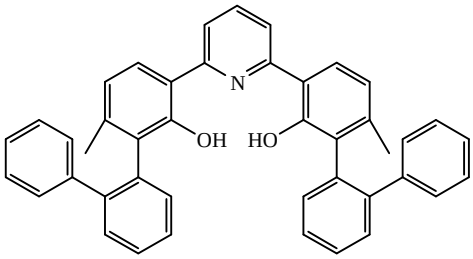
Scheme 165

Obviously, several other substrates, stoichiometric oxidizing agents and reaction conditions could be investigated in the hope of achieving high asymmetric inductions. Instead, we decided to turn our attention to the synthesis of other chiral complexes in which the axial chirality of the biphenyl fragment is more pronounced.

VI. 2. Complex 6.15

VI. 2. 1. Synthesis of ligand 6.9

A deeper analysis of the structure of the chiral ligand led us to believe that a marked size difference between the *ortho*-substituents of the biphenyl fragment would increase the asymmetric induction in the oxidations, as compared to ligand **6.1**. In view of this hypothesis, ligand **6.9** was chosen as the next chiral target. In this case, the axial rotation of the biphenyl fragment was blocked by only three *ortho*-substituents. Based upon our above described experiments, this substitution pattern has the advantage of being easier to synthesize as compared to biphenyl fragments that are substituted at all four *ortho* positions.

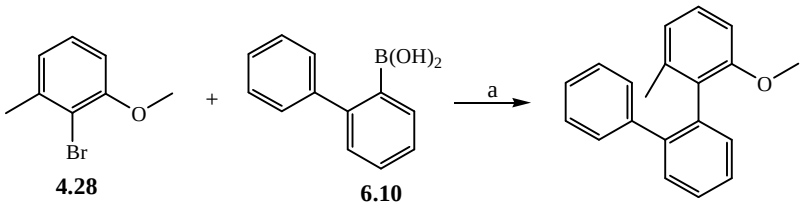


6.9

Scheme 166

We prepared methoxy-biphenyl **6.11** *via* a Suzuki coupling, applying the conditions found to be the most successful earlier for the model substrate (*Scheme 167, Table 13, Entry 1*). Since we obtained **6.11** in a very good yield under these conditions, we tried to decrease the amount of $Pd_2(dba)_3$, X-Phos, and boronic acid **6.10** to render the reaction more economic on larger scale preparation. Based on these rapid tests, carried out on 1 mmol scale, we could decrease considerably the amount of the palladium catalyst and its ligand.

However, since the conversion proved to be more sensitive to the amount of boronic acid **6.10**, we did not change the ratio of the starting materials for the large scale preparation. Carrying out the reaction on 10 mmol scale, under these modified conditions, led to quantitative conversions (*Entry 5*).



4.28 **6.10** **6.11**

a) K_3PO_4, $Pd_2(dba)_3$, X-Phos, toluene, 110°C, overnight.

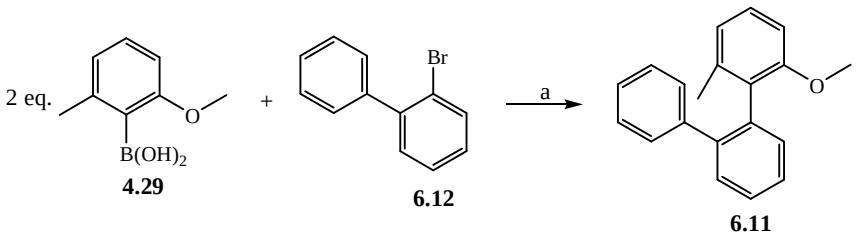
Scheme 167

Entry	**4.28** eq.	**6.10** eq.	K_3PO_4 eq.	$Pd_2(dba)_3$ mol%	X-Phos mol%	*Yield by NMR*
1	1	2	3	4	8	*87-100%*
2	1	2	3	2	4	*88%*
3	1	1.2	3	2	4	*74%*
4	1	1.2	3	1	2	*68%*
5[*]	1	2	3	1	2	*100%*

[*] Carried out on 10 mmol scale.

Table 13

Even though inverting the bromine and boronic acid fragments was disadvantageous in the case of the model substrate, the corresponding reaction on the real target was tested as well by sheer curiosity. In accordance with our previous experiences, **6.11** was obtained in a much lower yield in this coupling reaction (*Scheme 168*).



4.29 **6.12** **6.11**

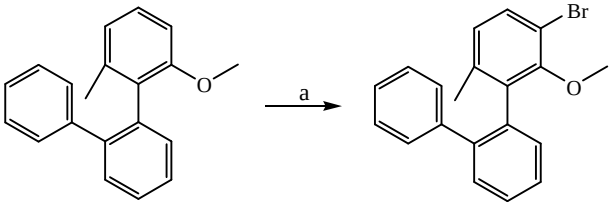
a) 3 eq. K_3PO_4, 4 mol% $Pd_2(dba)_3$, 8 mol% X-Phos, toluene, 110°C, overnight, 31%.

Scheme 168

Having obtained the biphenyl fragment **6.11** in excellent yields by the route depicted in *Scheme 167*, we turned our attention to the separation of its enantiomers. We found appropriate analytical HPLC conditions, but our equipments for the preparative scale did not allow the separation of more than 40 mg of substrate per injection. Finally, the enantiomers of **6.11** were separated on preparative scale by Véronique Pinilla at UCB Pharmaceuticals.

The synthesis was continued by testing initially each step on the racemic substrate. If no problem was encountered, the sequence was repeated with the (-)-enantiomer of **6.11**.

The corresponding brominated derivatives were prepared *via ortho*-lithiation in a surprisingly good yield, as compared to our original model substrate (*Scheme 169*).

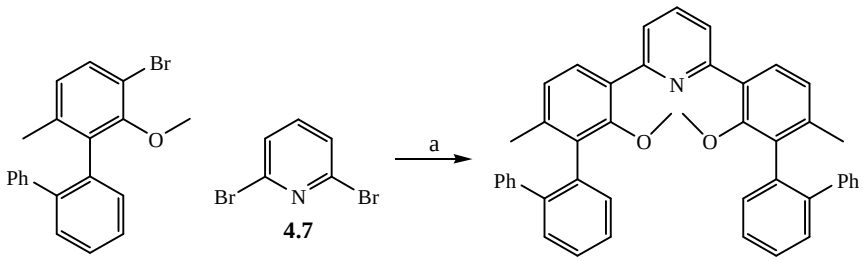


6.11 **6.13**

a) i. 2 eq. *n*-BuLi, 2 eq. TMEDA, ether (0.1M), 2h, RT;
ii. Br_2 in hexane, -78°C to RT, 54-65%.

Scheme 169

Unfortunately, **6.11** and **6.13** couldn't be separated easily and they had to be used as a mixture in the coupling step (*Scheme 170*). The corresponding Grignard reagent didn't form at all by the usual procedure, even upon refluxing overnight. Consequently, the recovered starting materials contained **6.11** and **6.13** in the same ratio as before the reaction.



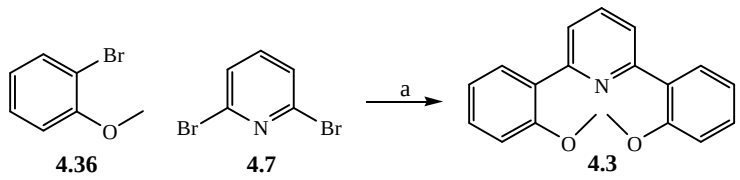
6.13 **4.7** **6.14**

a) i. Mg, THF, reflux, overnight; ii. 0.5 eq. **4.7**, 3 mol% $NiCl_2$dppe, 0°C to RT, overnight, 0%.

Scheme 170

At that point, we decided to prepare the organomagnesium species by transmetallation of the lithiated derivative. The feasibility of the coupling reaction under these conditions was first tested on our simple model (*Scheme 171* and *Table 14*). During the optimization studies, an important solvent effect was revealed. First of all, expecting that the synthesis of the brominated intermediate **6.13** would become unnecessary by using this route, and knowing that for the *ortho*-lithiation of **6.11** diethyl ether was the ideal solvent, we carried out the lithiation of the 2-bromo-anisole **4.36** in diethyl ether. However, since the coupling reaction was originally carried out in THF, we added a THF solution of magnesium-dibromide for the transmetallation, and the mixture of 2,6-dibromopyridine and $NiCl_2$dppe catalyst was added in THF as usual. Under these

conditions, the reaction didn't work at all at room temperature, and the conversion was low, even after refluxing the reaction mixture overnight (*Entry 1 and 2*). Increasing the amount of the catalyst to 10 mol% improved somewhat the yield, but it was still low compared to the original procedure (*Entry 3*). At that point, we thought that the presence of diethyl ether might have a negative influence on the nickel-coupling. However, carrying out the reaction exclusively in THF did not lead to any coupling at all (*Entry 4*). The reaction was repeated twice and the same result was obtained both times. Recognizing that the presence of diethyl ether is necessary for the reaction, we tested diethyl ether as the exclusive solvent, and observed the formation of **4.3** in *43%* yield (*Entry 5*). Since the yield was still moderate, we reasoned that some THF might be advantageous for the coupling step. Carrying out the lithiation and the formation of the organomagnesium species in diethyl ether, but adding the mixture of 2,6-dibromopyridine and $NiCl_2$dppe in THF, we could indeed increase the yield (*Entry 6*). Keeping the same strategy and the same final concentration, but decreasing the amount of diethyl ether and increasing the amount of THF, led to a final yield of *60%*. We were delighted to reach such a conversion and stopped the optimization. However, we have to mention that when the concentration of the reaction was doubled, the yield dropped significantly. Thus, by finding the ideal concentration and ratio of solvents, we could probably obtain similar yield as by the original procedure.



4.36 **4.7** **4.3**

a) i. *n*-BuLi, solvent, RT; ii. $MgBr_2$, solvent, RT; iii. 0.5 eq. **4.7**, $NiCl_2$dppe, solvent, 0°C to reflux, overnight.

Scheme 171

Entry	Solvents			Solvent ratio i/ii/iii	Catalyst mol%	Temp. iii	*Yield*
	i	ii	iii				
1	Et_2O	THF	THF	2/2/1	3.2	RT	-
2	Et_2O	THF	THF	2/2/1	3.2	67°C	*22%*
3	Et_2O	THF	THF	2/2/1	10	67°C	*38%*
4	THF	THF	THF	2/2/1	10	67°C	-
5	Et_2O	Et_2O	Et_2O	2/2/1	10	67°C	*43%*
6	Et_2O	Et_2O	THF	2/2/1	10	67°C	*48%*
7[a]	Et_2O	Et_2O	THF	2/2/1	10	67°C	*53%*
8[b]	Et_2O	Et_2O	THF	2/1/2	10	67°C	*60%*

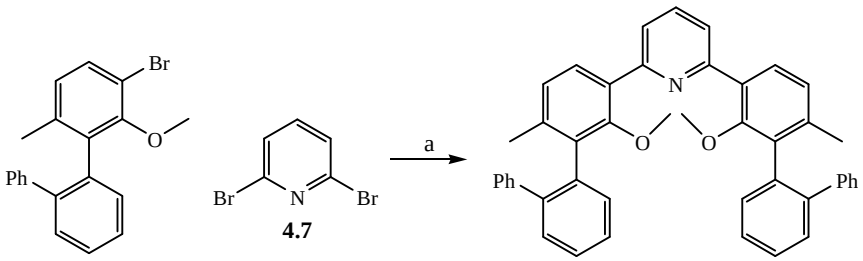
a) New bottle of $MgBr_2xEt_2O$ used. b) Same concentration for the coupling step as in Entry 7, but less Et_2O and more THF was used.

Table 14

From the above study, we can conclude that diethyl ether is the ideal solvent for the formation of the organomagnesium species by this method. However, for the nickel-coupling, a small amount of THF is advantageous. Concerning the solvent effect, it is interesting to note that by reacting **4.36** with magnesium powder, the formation of the Grignard reagent was complete within three hours at room temperature in THF, but it didn't occur at all in diethyl ether, even upon heating.

The optimized conditions were then applied to the synthesis of racemic and enantiopure **6.14** as well (*Scheme 172*). We think that the relatively low yield of **6.14** is due to the presence of **6.11**, which

obviously does not react, but alters the solubility issues. This hypothesis was supported by the fact that **6.14** was obtained in higher yield when the starting material contained lower amount of **6.11**. Dilution of the reaction mixture would probably be beneficial for the conversion. Unfortunately, little time was left and we couldn't optimize these conditions.

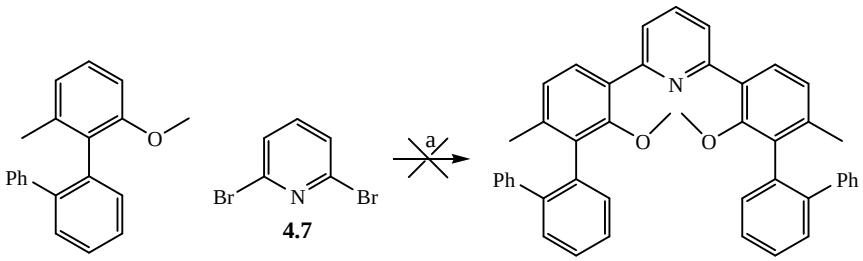


6.13 **4.7** **6.14**

a) i. *n*-BuLi, Et_2O, RT; ii. $MgBr_2xEt_2O$, Et_2O, RT; iii. 0.5 eq. **4.7**, 10 mol% $NiCl_2$dppe, THF, 0°C to 67°C, overnight, 13-24%.

Scheme 172

By employing the direct lithiation/magnesium exchange of compound **6.11**, we hoped to avoid the preparation of the bromo derivative **6.13**. However, using **6.11** as the starting material, the coupling didn't occur at all (*Scheme 173*).



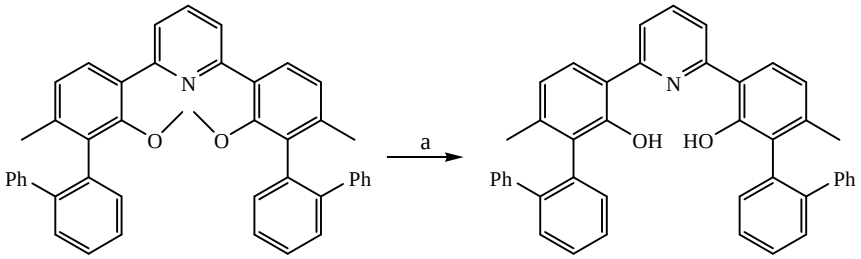
6.11 **4.7** **6.14**

a) i. *n*-BuLi, TMEDA, Et_2O, RT; ii. $MgBr_2xEt_2O$, Et_2O, RT; iii. 0.5 eq. **4.7**, 10 mol% $NiCl_2$dppe, 0°C to 67°C, overnight, 0%.

Scheme 173

A plausible explanation for the failure of this latter pathway could be the presence of TMEDA, which is required for the lithiation of **6.11**, but probably blocks the coupling reaction.

Cleavage of the hydroxyl protecting groups was successfully carried out (*Scheme 174*). Unfortunately, however, we didn't have a sufficiently high amount of ligand (-)-**6.9** for extensive further testing.



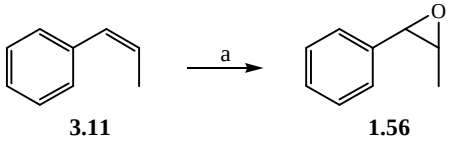
(–) 6.14 **(–) 6.9**

a) EtSH, $AlCl_3$, 0°C to RT, 2h, 62%.

Scheme 174

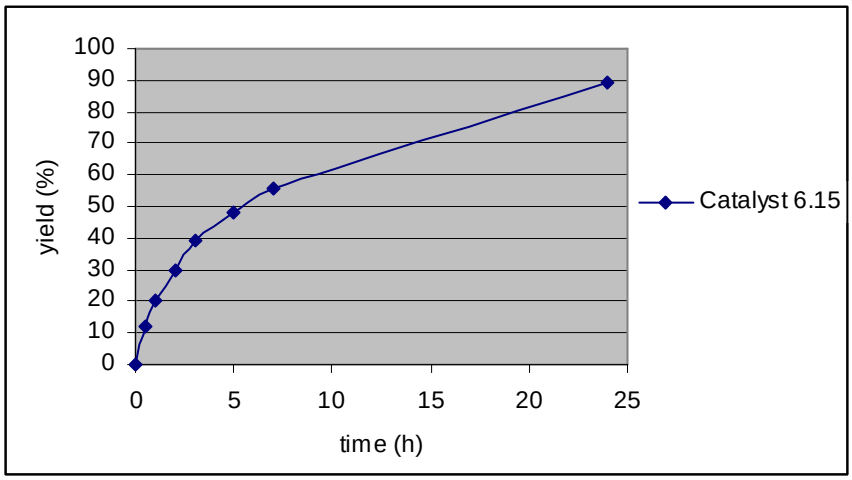
VI. 2. 2. Oxidation test by in situ formation of the catalyst

Possessing only a few mg of ligand (-)-**6.9**, we didn't try to isolate or characterize the corresponding molybdenum complex **6.15**. Nevertheless, a single oxidation test was carried out by forming the catalyst *in situ* from ligand (-)-**6.9** and $MoO_2(acac)_2$ before the addition of the substrate and the oxidizing agent (*Scheme 175*). Under these conditions, the stereospecific epoxidation of *cis-β*-methyl-styrene proceeded smoothly, but without providing any enantiomeric excess.



3.11 **1.56**

a) 1 mol% ligand **(–) 6.9**, 1 mol% $MoO_2(acac)_2$, 2 eq. *t*-BuOOH, DCE, 40°C.



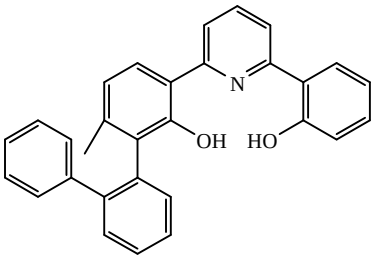
Scheme 175

We have to emphasize that the possible presence of the achiral $MoO_2(acac)_2$ makes this result difficult to compare with those obtained using isolated catalysts.

VI. 3. Complex 6.21

VI. 3. 1. Synthesis of ligand 6.16

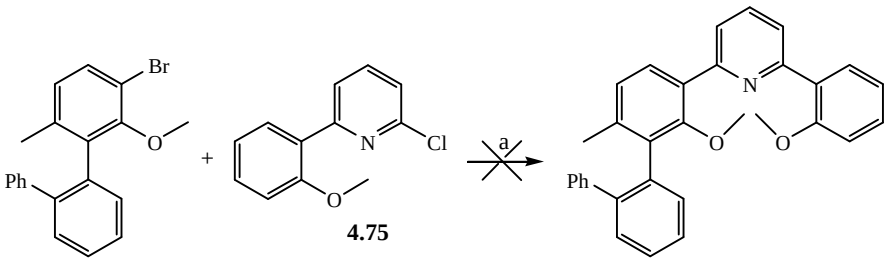
We decided to use the same biphenyl fragment **6.11** for the synthesis of a ligand asymmetrically substituted on its pyridine ring. Thus, ligand **6.16** became our next synthetic target (*Scheme 176*). As in case of the previous ligand, each step was tested on the racemic mixture and then, the operational sequence was repeated with the enantiopure fragment (+)-**6.11**.



6.16

Scheme 176

Having both **6.13** and **4.75** in hands from preceding synthesis, we tested them in the nickel-catalyzed coupling reaction (*Scheme 177*). However, the aryl chloride **4.75** proved to be unreactive under these conditions.

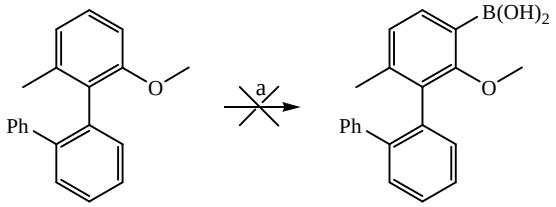


6.13 **4.75** **6.17**

a) i. *n*-BuLi, Et_2O, RT; ii. $MgBr_2xEt_2O$, Et_2O, RT; iii. 1 eq. **4.75**, 10 mol% $NiCl_2$dppe, THF, 0°C to 67°C, overnight, 0%.

Scheme 177

Then, we tried to prepare the boronic acid **6.18** in order to test the corresponding Suzuki coupling. However, the conditions applied before for the synthesis of other boronic acids were not successful in this case (*Scheme 178*).



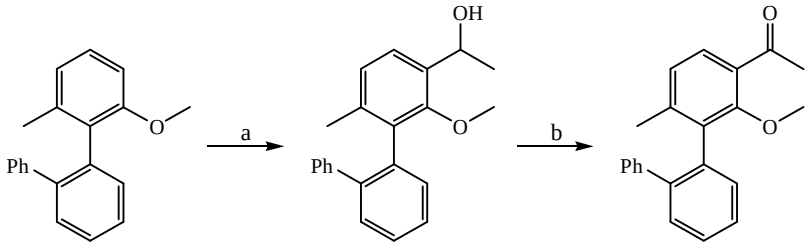
6.11 **6.18**

a) i. *n*-BuLi, TMEDA, Et_2O, RT; ii. $B(i\text{-}PrO)_3$, -78°C to RT; iii. HCl (aq.), 0%.

Scheme 178

After these initial attempts, our synthetic strategy was modified. In order to obtain ligand **6.16** more rapidly, for the oxidation tests, the longer but already operational pathway **A** was preferred.

Ketone **6.20** was easily prepared from **6.11** by the usual two step procedure (*Scheme 179*). Intermediate **6.19** contains an additional centre of chirality and, in the case of the racemic biphenyl fragment, the corresponding diastereomer pairs were separated by column chromatography, for analytical purposes only. Indeed, since this centre of chirality was to be eliminated in the next step, this separation was not necessary.

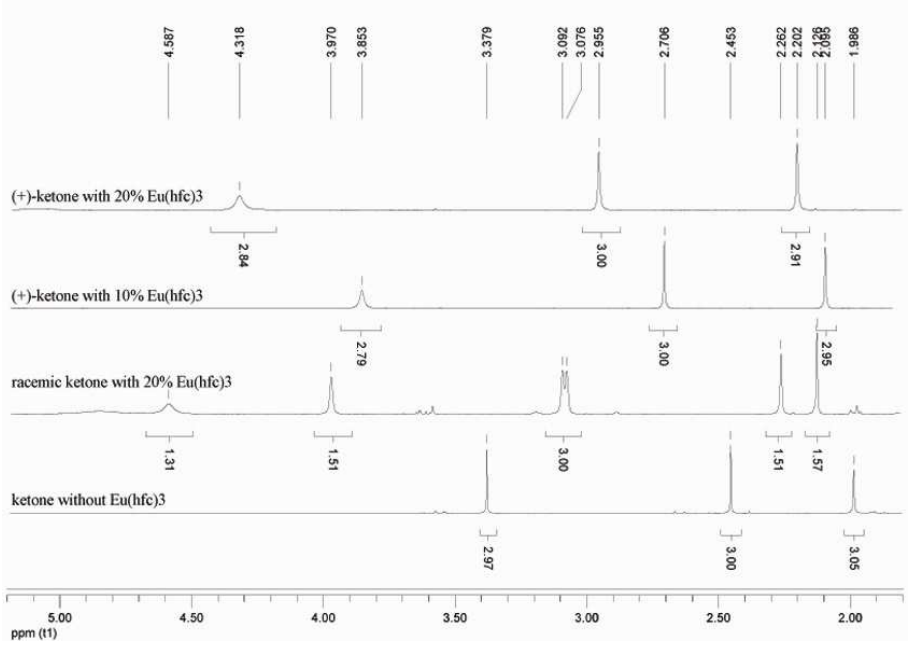


6.11 **6.19** **6.20**

a) i. *n*-BuLi, TMEDA, Et_2O, RT; ii. CH_3CHO, 0°C to RT, 44-49%; b) MnO_2, DCM, RT, 86-89%.

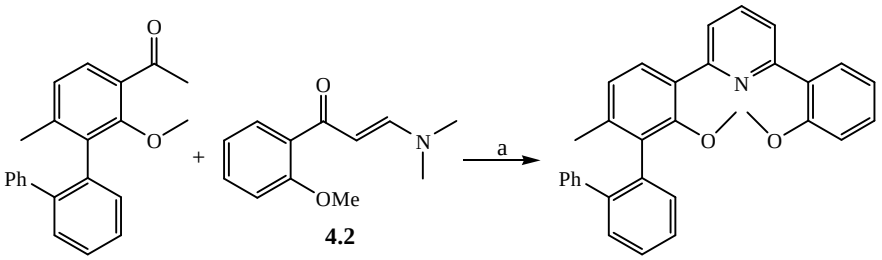
Scheme 179

With a sample of the racemic **6.20** also in hand, the enantiomeric purity of (+)-**6.20** could be confirmed by ^{1}H-NMR spectroscopy in the presence of Eu(hfc)$_3$ as the resolving agent (*Scheme 180*).



Scheme 180

Subsequently, we carried out the pyridine ring forming step using the previously synthesized enaminone **4.2** (*Scheme 181*). By performing the reaction on a 2 mmol scale, with the enantiopure ketone, (+)-**6.17** could be obtained in *76%* yield. We have to mention however, that on lower scale, **6.17** was generated in somewhat reduced yields.

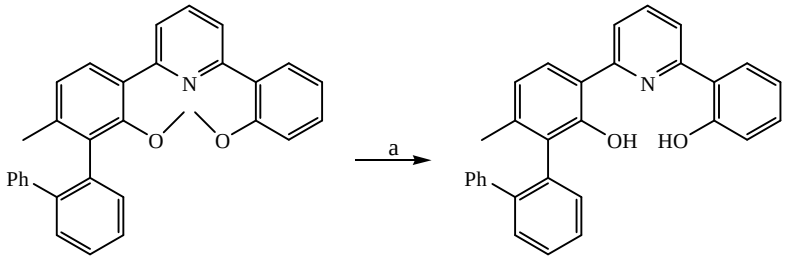


6.20 **4.2** **6.17**

a) i. NaH, THF, RT; ii. **4.2**, 24h, RT; iii. NH_4OAc, AcOH, 110°C, 2h, 43-76%.

Scheme 181

The cleavage of the hydroxyl protecting groups proceeded smoothly as well (*Scheme 182*). Thus, the enantiopure ligand (+)-**6.16** was obtained in a sufficient amount for further tests.



6.17 **6.16**

a) EtSH, $AlCl_3$, 0°C to RT, 2h, 52-70%.

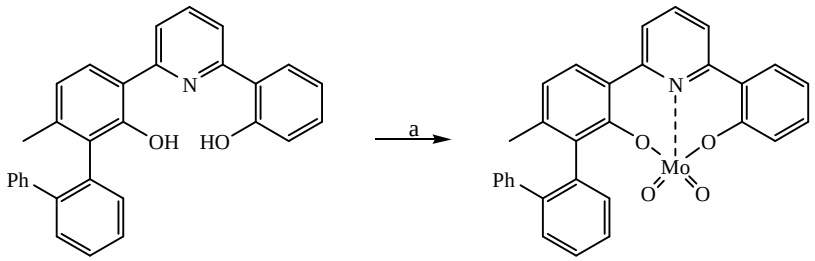
Scheme 182

VI. 3. 2. Complexation

The ligand exchange reaction between $MoO_2(acac)_2$ and ligand (+)-**6.16** was not complete under the usual reaction conditions (DCM, room temperature). Additionally, the complex thus generated could not be separated efficiently from the unreacted $MoO_2(acac)_2$.

Fortunately, we found that much higher conversion could be reached by carrying out the reaction in methanol (*Scheme 183*). By using equimolar amounts of $MoO_2(acac)_2$ and ligand (+)-**6.16**, and

removing the liberated 2,4-pentanedione by repeated evaporation of diethyl ether and methanol from the crude mixture, led to complete conversion. Thus, complex (+)-**6.21** could be isolated in high yield and in pure form as a lemon yellow powder.



(+) 6.16 **(+) 6.21**

a) $MoO_2(acac)_2$, MeOH, RT.

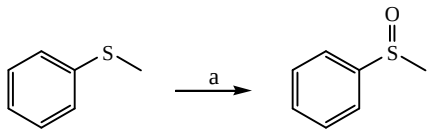
Scheme 183

Having prepared the complex in methanol, we could expect the presence of a solvent molecule at the sixth coordination site around the molybdenum centre. The lemon yellow colour of the isolated complex is in accordance with the six-coordinated geometry based upon our previously described hypothesis.

Complex (+)-**6.21** was analyzed by standard spectroscopic methods. Similarly to complex (+) or (-)-**6.8**, the ^{1}H and ^{13}C-NMR spectra did not show the presence of different diastereomeric forms. Additionally, the two strong bands at 941 cm^{-1} and 914 cm^{-1} found in the IR spectrum are characteristic for mononuclear, molybdenum *cis*-MoO_2 complexes.

VI. 3. 3. Oxidation tests

With the isolated complex in hand, the first oxidation tests were carried out on thioanisole (*Scheme 184* and *Table 15*). As in previous experiments, 1 mol% of catalyst and one equivalent of *t*-butyl-hydroperoxide were employed. These initial tests were carried out at 0°C and at -20°C. And, in addition to dichloromethane, only acetonitrile was tested as another solvent.



5.3 **2.14**

a) 1 mol% catalyst (+)-**6.21**, 1 eq. *t*-BuOOH.

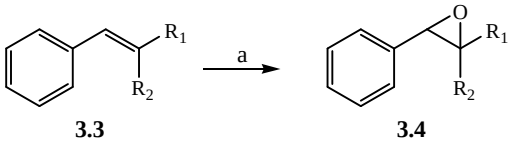
Scheme 184

Entry	Solvent	Temperature	Reaction time	*Conversion*	*ee*
1	DCM	0°C	7h	*75%*	*0%*
2	DCM	-20°C	7h	*53%*	*0%*
3	MeCN	0°C	7h	*68%*	*0%*
4	MeCN	-20°C	7h	*38%*	*0%*

Table 15

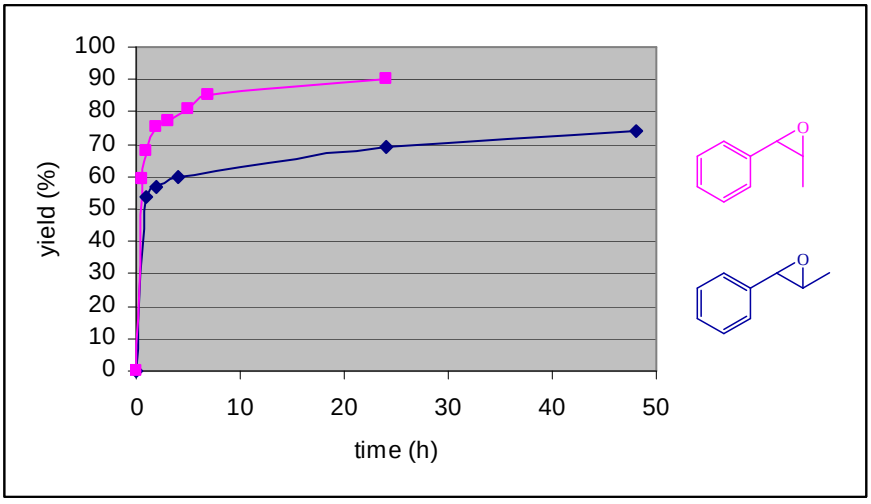
Catalyst (+)-**6.21** proved to be active under these conditions, giving the sulfoxide as the sole oxidation product. Unfortunately, however, it did not lead to any asymmetry in the reaction.

The epoxidations of *cis*- and *trans*-*β*-methyl-styrene have been performed as well, using the catalyst (+)-**6.21** (*Scheme 185*).



3.3 **3.4**

a) 1 mol% catalyst (+)-**6.21**, 2 eq. *t*-BuOOH, DCE, 40°C



Scheme 185

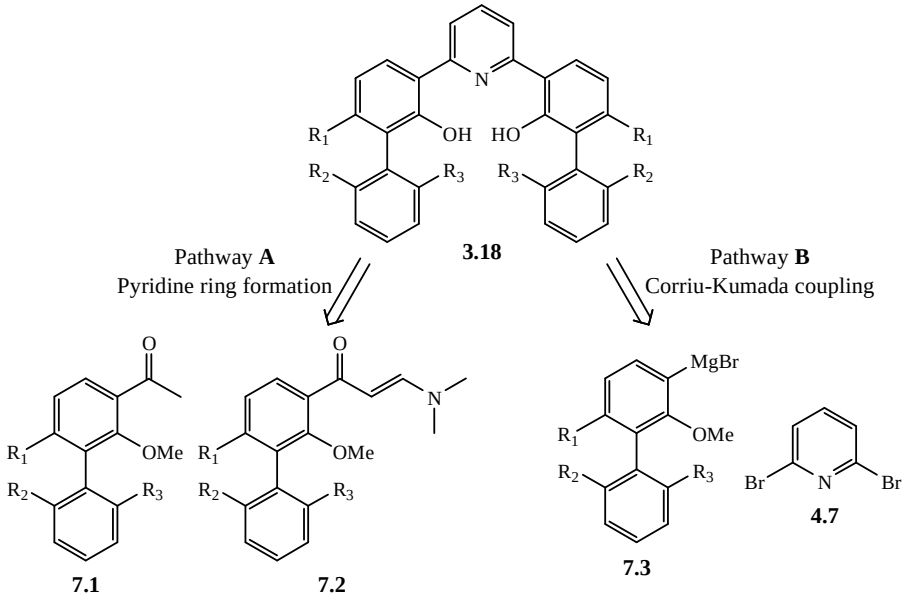
Remarkably, the epoxidation of the *cis* alkene was somewhat faster and proved to be completely stereospecific, giving the *cis* epoxide exclusively. Regrettably, however, no enantiomeric excess could be obtained in these initial oxidation tests.

At this stage, we decided to stop our investigation on these pyridine-type ligands and leave it to another researcher to fully evaluate their potential.

VII. Conclusions

VII. 1. Ligand synthesis

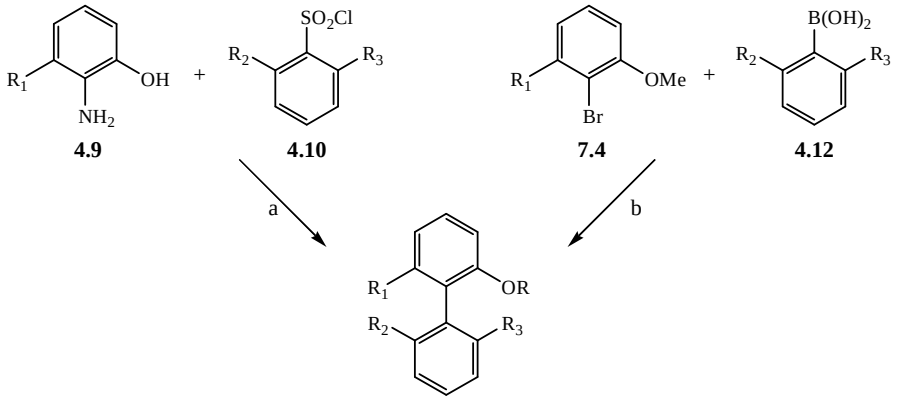
Two fundamentally different synthetic strategies have been established for the formation of the ligand skeleton **3.18** (*Scheme 186*). The formation of the pyridine ring from the ketone and the enaminone fragments proved to be a bit longer but high yielding (pathway **A**). In contrast, the success of pathway **B** depended on the efficient formation of the organomagnesium species. Applying appropriate phenol protecting groups was shown to be essential in the case of both pathways.



Scheme 186

The formation of the tetra-*ortho*-substituted biphenyl intermediates **7.5** was shown to be successful by the three-step procedure of Motherwell using 2-hydroxy-amines **4.9** and sulfonyl chlorides **4.10** as starting materials (*Scheme 187*). In stark contrast, the

Suzuki-Miyaura cross coupling reaction gave low yields for the tetra-*ortho*-substituted biphenyls **7.6**. Importantly however, good to high yields were achieved under these conditions for tri-*ortho*-substituted biphenyls ($R_1 \neq R_3 = H$). Additionally, lower yields have been obtained when the boronic acid fragments held the methoxy function.



4.9 **4.10** **7.4** **4.12**

7.5 R=H
7.6 R=Me

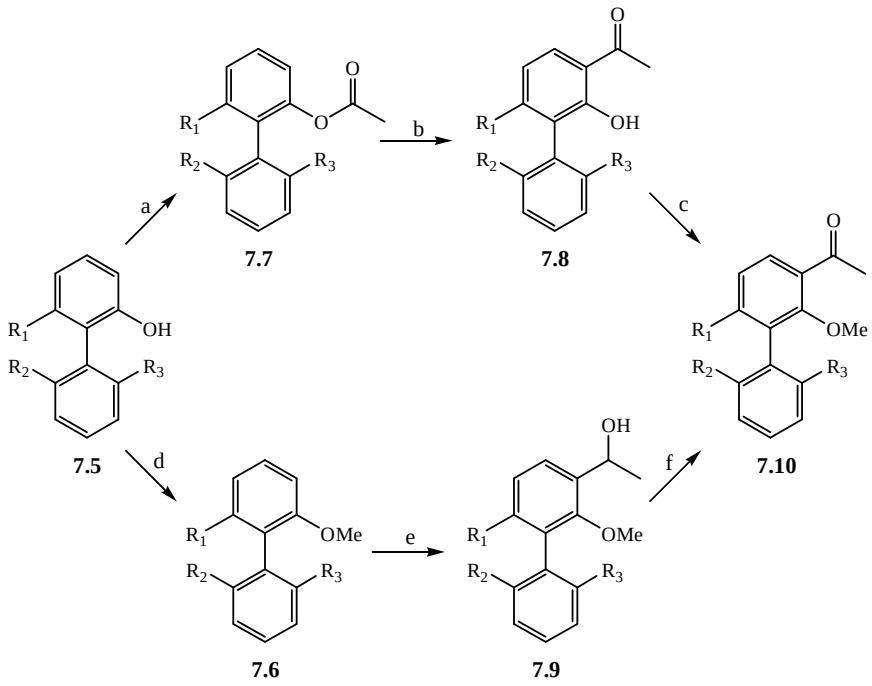
a) i) Et_3N, DCM, 0°C to RT; ii) HBF_4, *i*-$C_5H_{11}ONO$, EtOH, 0°C; iii) $TiCl_3$, $HCl_{(aq.)}$, acetone, 0°C.
b) $Pd_2(dba)_3$, X-Phos, K_3PO_4, toluene, 110°C.

Scheme 187

Tetra- and tri-*ortho*-substituted biphenyls **7.5** and **7.6** were common intermediates of pathway **A** and **B**.

Two procedures have been found to obtain ketones **7.10** (*Scheme 188*). Whilst the conditions of the Fries rearrangement of acylated intermediates **7.7** were not optimized, the *ortho*-lithiation of the methoxy-biphenyls **7.6**, followed by the addition of acetaldehyde, resulted in the formation of alcohols **7.9**, which were further oxidized to obtain the corresponding ketones **7.10**. We have to mention that *ortho*-lithiation of **7.6** proved to be more difficult compared to the non-substituted anisole. While looking for the appropriate conditions, we could take advantage of the much easier *ortho*-lithiation of the

methoxy-methyl protected form. In this case, however, the methoxy-methyl protecting group had to be changed after the formation of the ketone, since it was not suitable for the key step of the synthesis.

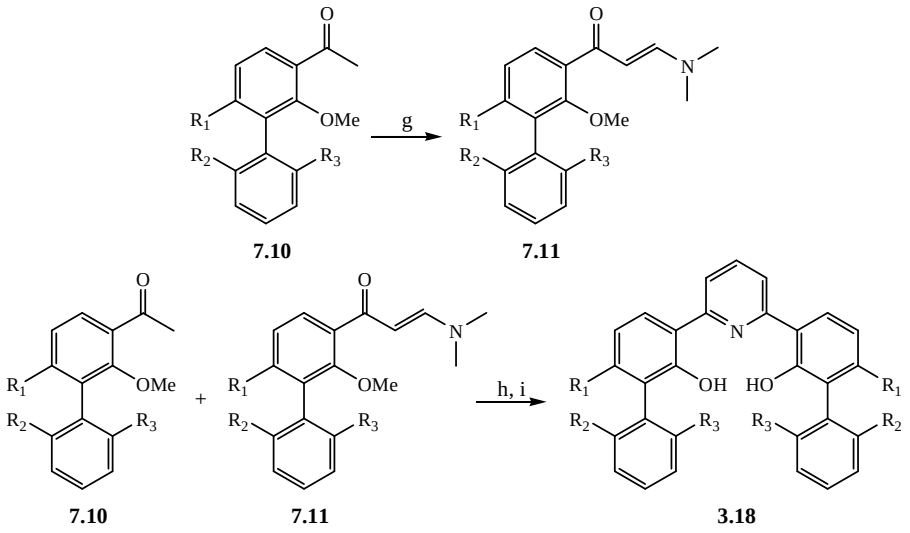


a) Et_3N, CH_3COCl, DCM, 0°C to RT; b) $AlCl_3$, PhCl, 140°C; c) K_2CO_3, Me_2SO_4, acetone, reflux; d) MeI, KOH, DMSO, RT; e) *n*-BuLi, TMEDA, ether (0.1 M), RT, then CH_3CHO, 0°C to RT; f) 5 mol% CuCl/1,10-phenantroline/*t*-BuOK/DBAD, O_2, C_6H_5F, 80°C or MnO_2, DCM, RT.

Scheme 188

Enaminones **7.11** have been successfully obtained by the transformation of ketones **7.10** and the key step of pathway **A** was carried out (*Scheme 189*). Applying ketones and enaminones derived from the same biphenyl fragments gave access to symmetrically substituted diaryloxy-pyridines. Additionally, using differently substituted ketones and enaminones, the synthesis of asymmetrically substituted diaryloxy-pyridines could be carried out as well. Importantly, an efficient method that did not require elevated

temperature has been found for the cleavage of the hydroxyl protecting groups.



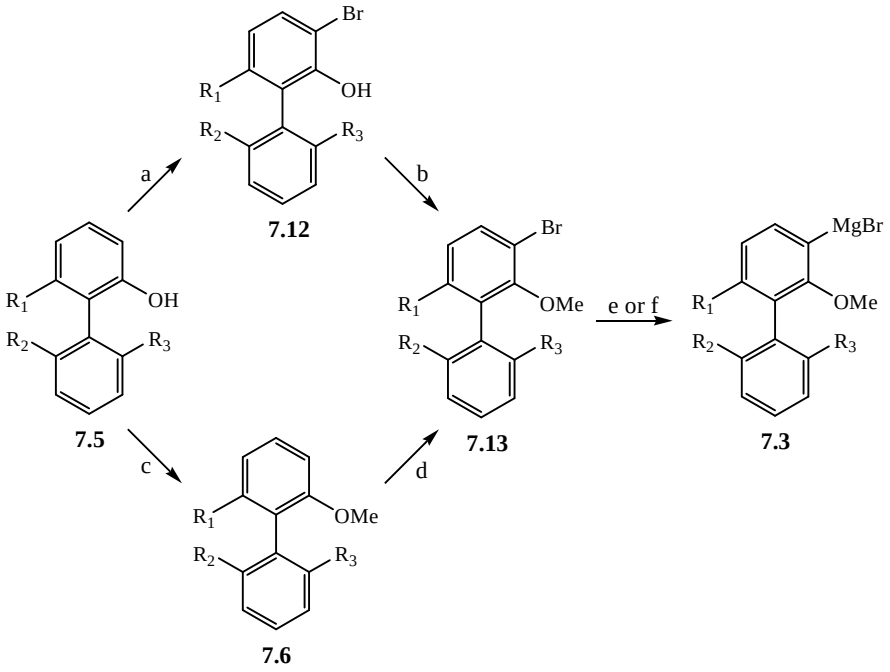
g) $Me_2NCH(OMe)_2$, 110°C; h) i. **7.10**, NaH, THF, RT; ii. **7.11**, RT; iii. NH_4OAc, AcOH, 110°C; i) $AlCl_3$, EtSH, 0°C to RT.

Scheme 189

Concerning pathway **B**, the bromides **7.13** were either prepared by the low-temperature *ortho*-bromination of phenol **7.5** and a subsequent protection of the hydroxyl function, or by bromination of **7.6** *via* the *ortho*-lithiated intermediate (*Scheme 190*). Generally, the first method had the advantage of higher yields and more efficient enantiomer separation in the case of chiral ligand synthesis.

The corresponding Grignard reagents were usually prepared by reacting bromides **7.13** with magnesium powder. Depending on the reactivity of the given bromide, the reaction could be carried out at room temperature or needed reflux. In one special case, the bromide refused to react with the magnesium powder, even at elevated temperature, and therefore, an alternative protocol has been developed for the formation of the organomagnesium species. This latter method

involved the generation of a lithiated intermediate by bromine-lithium exchange, and a subsequent transmetallation using magnesium bromide. It is noteworthy that the preparation of the brominated intermediate **7.13** could not be avoided, since the required special conditions for the *ortho*-lithiation of **7.6** did not allow its direct use in the coupling reaction. Probably, in that case, it was the presence of the coordinating TMEDA which blocked either the formation of the organomagnesium species or the nickel-coupling.



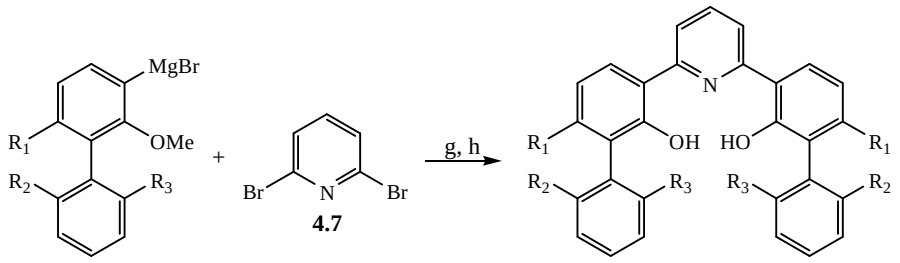
a) *t*-$BuNH_2$, Br_2, toluene, -78°C to RT; b) K_2CO_3, Me_2SO_4, acetone, reflux; c) MeI, KOH, DMSO, RT; d) *n*-BuLi, TMEDA, ether (0.1 M), RT, then Br_2 in hexane, -78°C to RT; e) Mg, THF, RT or reflux; f) *n*-BuLi, $MgBr_2xEt_2O$, ether, RT.

Scheme 190

The obtained organomagnesium species were successfully employed in the key step of pathway **B** (*Scheme 191*). Preparing the organomagnesium species by the transmetallation protocol, an important solvent effect has been revealed. While diethyl ether was

the solvent of choice for the formation of the Grignard reagent, a small amount of THF was advantageous for the coupling step.

Finally, cleavage of the hydroxyl protecting groups furnished the required ligands.



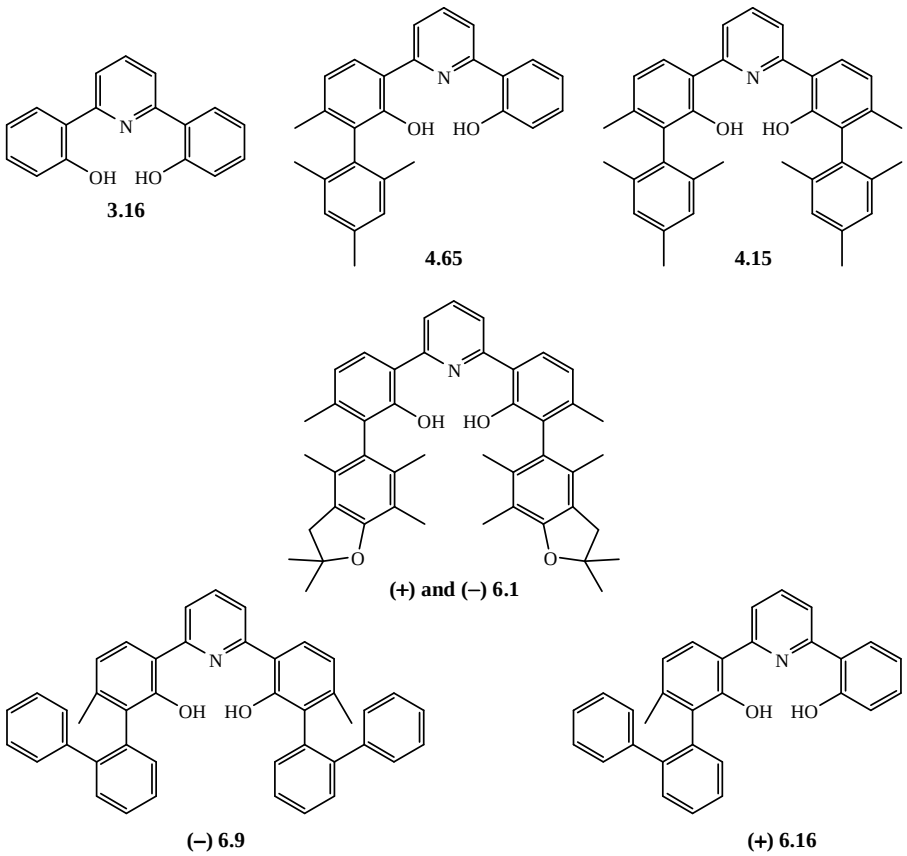
7.3 **4.7** **3.18**

g) $NiCl_2$dppe, THF, 0°C to 67°C; h) $AlCl_3$, EtSH, 0°C to RT.

Scheme 191

The above described synthetic pathways have been developed during the synthesis of the achiral model ligands **3.16**, **4.65** and **4.15** and then successfully applied to the formation of chiral, enantiopure ligands (+) and (-)-**6.1**, (-)-**6.9** and (+)-**6.16** (*Scheme 192*). For the synthesis of these chiral ligands, enantiopure biphenyl fragments were used separating the enantiomers of the appropriate biphenyl intermediates.

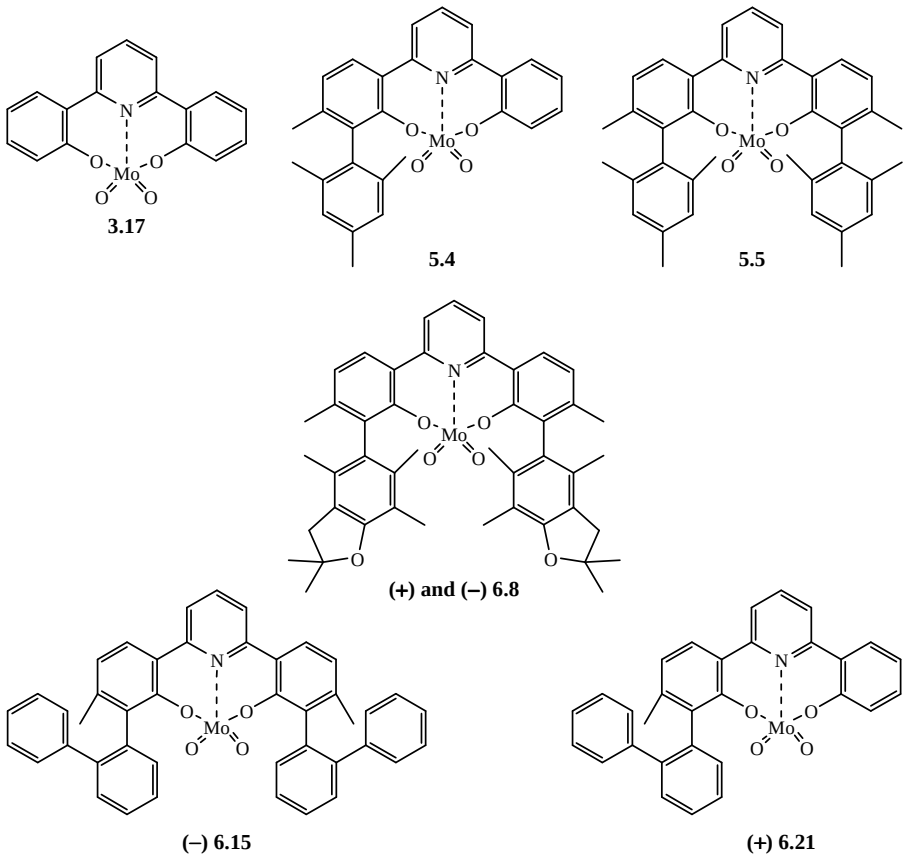
It is important to emphasize that pathway **A**, not only gives us the possibility to synthesize easily the asymmetrically substituted pyridines, but it can also be applied as a complementary method for the preparation of symmetrically substituted pyridines, when the formation of the Grignard reagent, required for the shorter pathway **B**, is a problem.



Scheme 192

VII. 2. Complexes

Molybdenum complexes of the above presented ligands have been prepared by ligand exchange reactions using $MoO_2(acac)_2$ as the metal source. Due to varying steric and solubility properties, the complexation, isolation and purification procedures had to be adjusted to the given substrates. Because ligand (-)-**6.9** was only synthesized in small amount, its molybdenum complex was exceptionally not isolated and characterized.



Scheme 193

In all the other cases, the structure of the isolated complexes was fully elucidated by NMR, Mass and IR spectoscopies. Additionally, complexes **3.17**, **5.5**, and δ-(+)-(*S*,*S*)-**6.8** were successfully crystallized and the unambiguous determination of their structure was performed by single crystal X-ray analysis. The crystalline complexes were shown to be mononuclear and to contain the *cis*-MoO_2 structural unit of the parent complex. All of the ligands we synthesized coordinated to the molybdenum centre by their three donor heteroatoms. Additionally, a solvent molecule, originating from the crystallization procedure, is coordinated to the metal centre, thereby completing the distorted tetragonal bipyramidal complex

geometry. The phenolic oxygens are positioned diagonal to each other, one above and the other one below the plane of the pyridine ring. This structural feature suggested to us the existence of two enantiomeric forms in the case of the achiral ligands. However, the stability of these enantiomeric forms could not be determined. On the other hand, complexation of the chiral ligands was either totally diastereoselective or the diastereomeric forms couldn't be differentiated by NMR spectroscopy.

VII. 3. Oxidation tests

All of the molybdenum complexes were shown to be active epoxidation and sulfoxidation catalysts. Unfortunately, the optically active complexes did not introduce asymmetry under our reaction conditions.

In general, electron rich sulfides, alkenes and allylic alcohols were oxidized faster than styrene derivatives or terminal alkenes. Geraniol was regioselectively oxidized at the double bond proximal to the hydroxyl function. Additionally, epoxidation of 1,2-disubstituted alkenes was shown to be completely stereospecific.

An interesting structure-reactivity relationship has been established by comparing the activity of complexes **3.17**, **5.4** and **5.5** during the epoxidation of *trans*-β-methyl-styrene and 1-octene. Increasing the size of the catalyst increased the reactivity of the molybdenum complex in these reactions. On the other hand, in the case of more electron rich substrates, the three catalysts showed similar reactivity.

This structure-activity relationship is either a result of the increasing potential for π-π interactions between the approaching olefin and the greater and greater aromatic cavity, or a consequence of the partial dissociation of the tridentate ligand. This dissociation should be more important for the bulkier catalysts.

The partial de-coordination of the tridentate ligands can also be detrimental to the asymmetric induction when using our optically active catalysts.

Additionally, based upon the X-ray diffraction analyses, while the perpendicular phenyl rings form small walls around the site of the oxidation directing the approach of the substrate, the ‘upper’ part of the catalyst, containing the pyridine and the two phenol rings, is rather flat. Blocking the approach of the substrate from these directions might be advantageous for asymmetric induction.

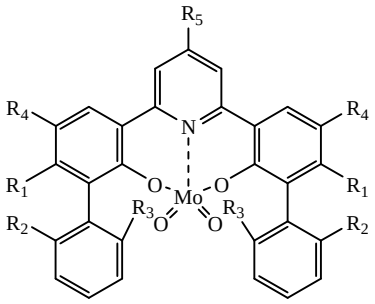
These hypotheses, concerning the lack of asymmetric inductions using our optically active catalysts, lead directly to our perspectives.

VIII. Perspectives

First of all, a more extensive testing of our optically active catalysts should be carried out using other stoichiometric oxidizing agents and different solvents and temperatures.

After scaling up the synthesis of the optically pure ligand **6.9**, the corresponding molybdenum complex should be prepared, isolated, characterized and fully investigated as a potential enantioselective oxidation catalyst.

As further perspective, the steric hindrance of the rather flat pyridine and phenol rings should be increased to guide better the approach of the substrate and oxidizing agent. For that, sterically demanding R_4 and R_5 groups should be attached as shown in *Scheme 194*.



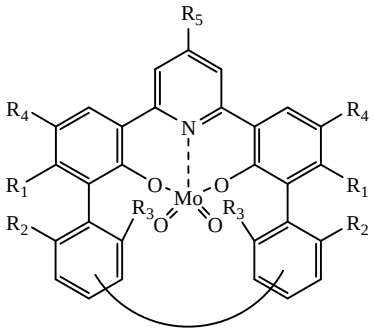
8.1

Scheme 194

Additionally, electron donating groups placed at these positions will probably increase the stability of the complex by strengthening the Mo-O and Mo-N bonds, and thus, decreasing the possibility of ligand de-coordinations.

The position of the R_5 group would be ideal for linking the catalyst to a surface as well.

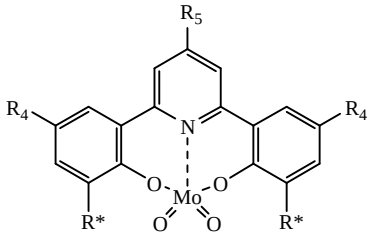
Linking the two biphenyl fragments to each other with an ideally long and flexible bridge, might also prevent the ligand detachment (*Scheme 195*).



8.2

Scheme 195

Furthermore, in place of the axial chirality, other chiral elements could be appended next to the site of oxidation (*Scheme 196*).



8.3

Scheme 196

As mentioned earlier, ligand **3.16** and its closely related derivatives, have been shown to form Cu(II), Al(III), Fe(III), Ti(IV) or Zr(IV) complexes. It would be interesting to study the asymmetric

induction of our enantiopure ligands in combination with these and other metals in a variety of metal catalyzed transformations.

IX. Experimental part

IX. 1. Instrumentation

Routine nuclear magnetic resonance (NMR) spectra were recorded on a Varian Gemini-2000 (^{1}H: 300 MHz and ^{13}C: 75 MHz) and a Bruker AC-300 Avance II (^{1}H: 300 MHz and ^{13}C: 75 MHz). High field spectra were recorded on a Bruker AM-500 (^{1}H: 500 MHz and ^{13}C: 125 MHz). All spectra were internally referenced to residual *protio* solvent signals, *i.e.* 7.26 for chloroform. Data for ^{1}H-NMR are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant (Hz), integration and assignment. Data for ^{13}C-NMR spectra are reported in terms of chemical shift (ppm) and assignment.

Infrared (IR) spectra were performed on a Perkin Elmer 681 spectrometer and a Shimadzu FTIR-8400S spectrometer. The samples were analysed as formulated KBr pastilles or thin films deposited on a NaCl plate (Perkin Elmer 681) or a ZnSe crystal (Shimadzu FTIR-8400S). Data of IR spectra are reported in terms of frequency of absorption (cm^{-1}), and peak intensities are described as follows: s = strong, m = medium, w = weak, b = broad.

Low-resolution mass spectra were recorded on Varian MATT-44 and Finningan MAT-TSQ 70 spectrometers with chemical ionisation (CI, 100 eV, ionisation gas: isobutane), atmospheric pressure chemical ionisation (APCI, 100 eV, ionisation gas: isobutane) and electrospray ionisation (ESI). Data are reported as follows: m/z, assignment, relative intensity.

High resolution mass spectra were performed on Thermo Finnigan MAT900XP (CI and EI) and on Waters LCT Premier XE (ESI) at the Mass Spectrometry Facility of the University College of London by Dr Lisa D. Harris.

Elemental analyses were performed at the Chemical Research Centre of the Hungarian Academy of Science at Budapest by Dr. Zsuzsanna Riedl.

Optical rotations were measured on Perkin Elmer 241 MC polarimeter with a 1 dm cell (1 ml) using a sodium lamp (589 nm).

X-ray analyses were performed by Prof. Bernard Tinant (Unité de chimie structurale et des mécanismes réactionnels, UCL, Louvain-la-Neuve), Bernadette Norberg and Prof. Johan Wouters (Groupe de chimie physique théorique et structurale, FUNDP, Namur).

Gaz chromatographies were carried out on Thermo Finnigan Trace GC and on Carlo Erba Instrument GC8000. Varian capillary column CP-Sil 5 CB (30m*0.25 mm*0.25 µm) was used for achiral analyses and Varian capillary column CP-Chirasil-Dex CB (25m*0.25 mm*0.25 µm) or chiraldex GTA Aspec (30m*0.25 mm*0.25 µm) for chiral analyses.

High performance liquid chromatography (HPLC) analyses were done with the following apparatus: two Gilson-306 pumps, a Gilson-805 manometric module, a Gilson-811D dynamic mixer, a Rheodyne-7725i injector, a Gilson UV-VIS-155 detector and/or a Dedl Sedex45 detector (20°C, N_2 pressure: 2 bars). Columns and solvent systems are specified for each analyzed compound later in the experimental part.

IX. 2. Techniques

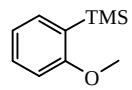
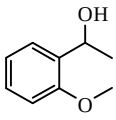
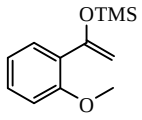
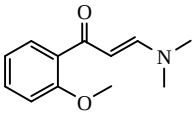
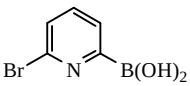
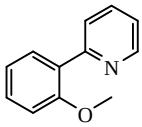
Thin-layer chromatographies (TLC) were performed on TLC aluminium sheets coated with Silica gel 60 F_{254} (Merck). The plates were visualised using ultra-violet light (256 nm) and developed using $KMnO_4$ or vanillin.

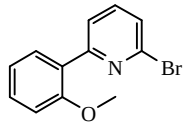
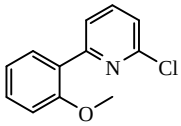
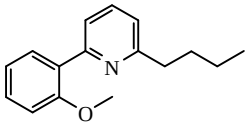
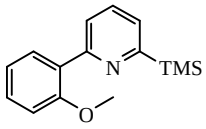
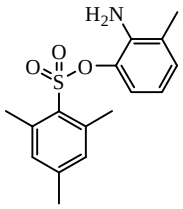
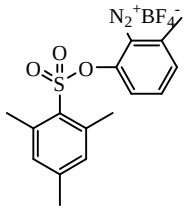
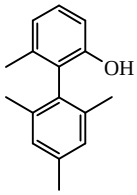
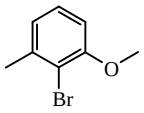
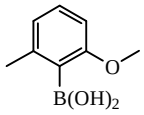
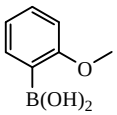
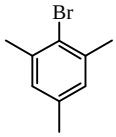
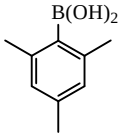
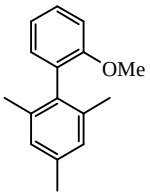
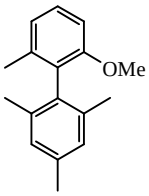
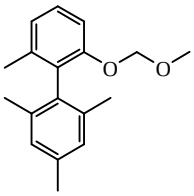
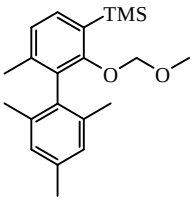
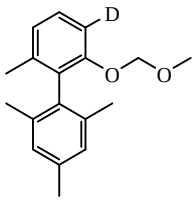
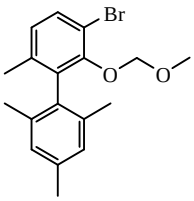
Flash chromatographies were performed using Merck Silica Gel 60 (230-400 mesh) under pressure with the stated solvents.

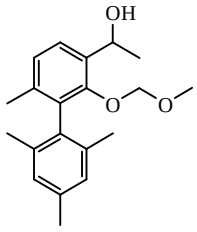
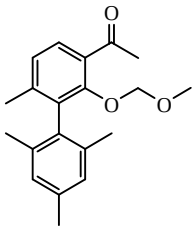
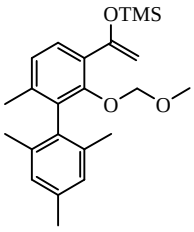
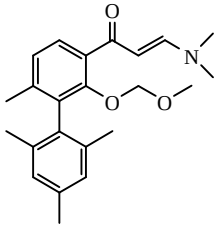
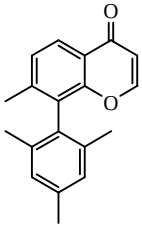
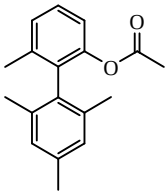
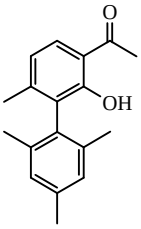
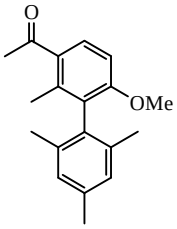
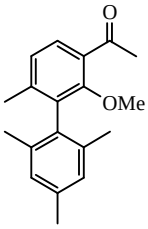
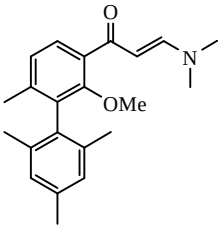
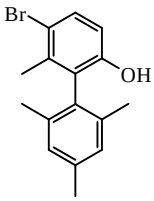
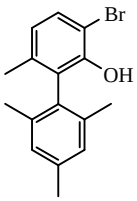
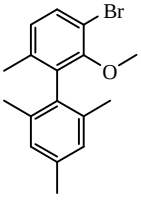
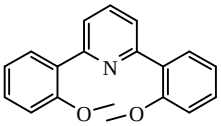
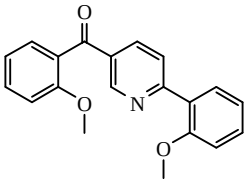
Solvents were of technical grade and distilled prior to use. Diethyl ether and tetrahydrofuran were distilled over sodium/benzophenone. Dichloromethane, dichloroethane, toluene, acetonitrile and triethylamine were distilled over CaH_2. Degassed solvents were prepared by three “freeze/pump/thaw” cycles.

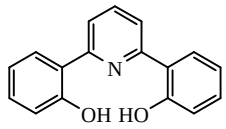
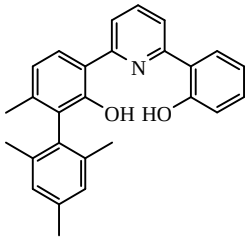
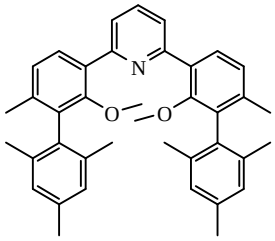
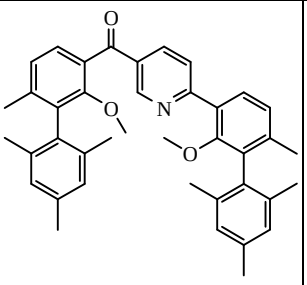
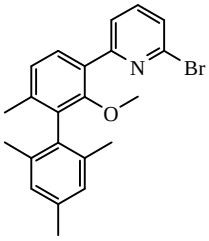
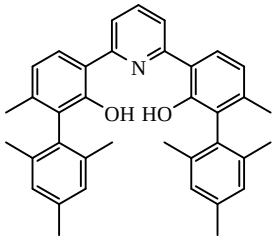
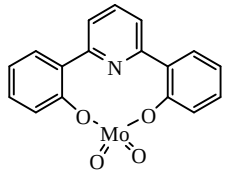
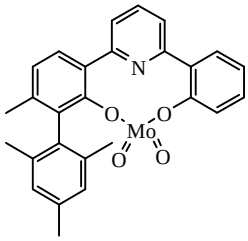
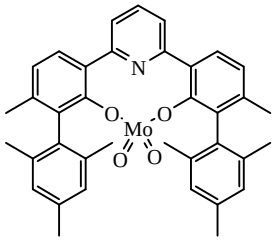
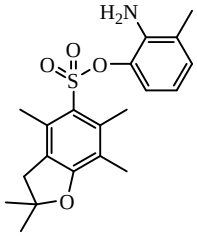
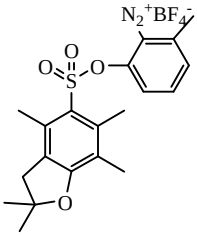
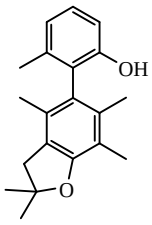
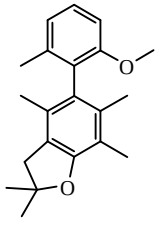
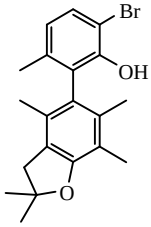
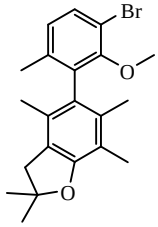
All commercially available compounds (Acros, Aldrich, Fluka and Lancaster) were used as received unless otherwise stated. All reactions were carried out under an atmosphere of argon, in flame-dried apparatus and with magnetic stirring, unless otherwise indicated.

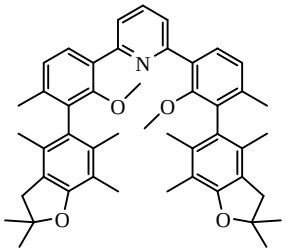
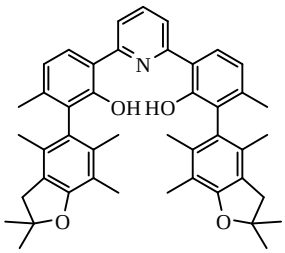
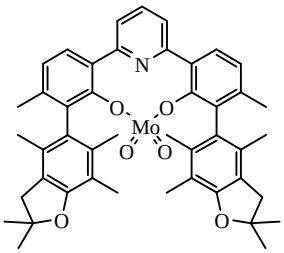
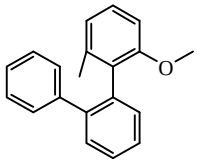
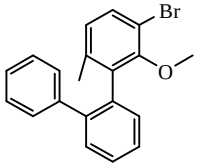
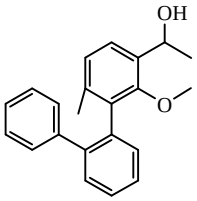
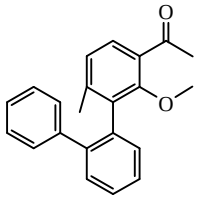
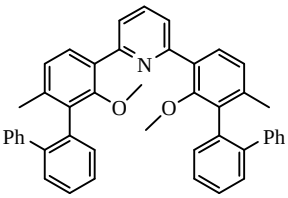
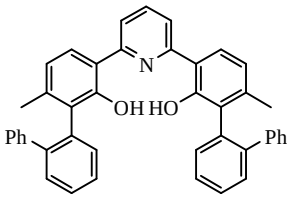
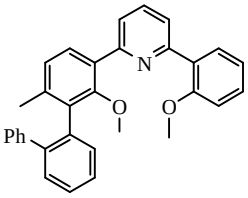
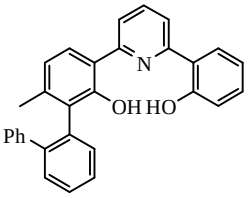
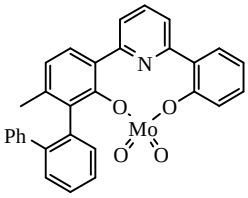
IX. 3. Structure index of synthesized compounds

 Page 205	 Page 206	 Page 208
 Page 209	 Page 211	 Page 212

 Page 214	 Page 217	 Page 218
 Page 220	 Page 221	 Page 223
 Page 225	 Page 226	 Page 228
 Page 229	 Page 231	 Page 232
 Page 234	 Page 236	 Page 238
 Page 240	 Page 242	 Page 244

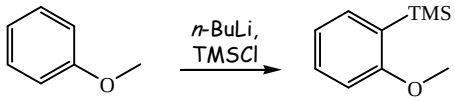
 Page 246	 Page 248	 Page 251
 Page 252	 Page 255	 Page 257
 Page 259	 Page 261	 Page 263
 Page 265	 Page 267	 Page 269
 Page 271	 Page 273	 Page 277

 Page 278	 Page 280	 Page 283
 Page 287	 Page 289	 Page 291
 Page 294	 Page 296	 Page 298
 Page 300	 Page 302	 Page 304
 Page 306	 Page 308	 Page 310

 Page 312	 Page 315	 Page 317
 Page 320	 Page 327	 Page 322
 Page 325	 Page 328	 Page 330
 Page 332	 Page 335	 Page 337

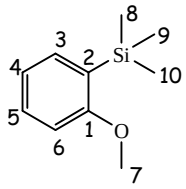
IX. 4. Experimental procedures

IX. 4. 1. Preparation of (2-methoxyphenyl)trimethylsilane



Anisole (110 µl, 1 mmol, 1 eq.) was added to dry, freshly distilled THF (1 ml) in a dry, two-necked flask (10 ml), under argon. *n*-BuLi (625 µl, 1.6 M in hexane, 1 mmol, 1 eq.) was added dropwise

at room temperature. The colour of the reaction mixture turned to yellow then orange. After six hours stirring, TMSCl (250 µl, 2 mmol, 2 eq.) was added dropwise. The mixture turned to white and blurry. After 30 minutes stirring, water was added and the mixture was extracted by diethyl ether. The separated organic phase was dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash column chromatography using petrol ether as eluent (R_f = 0.52) to obtain the title compound as a pure product (161 mg, *89%* yield).



Registry number: 704-43-8

Molecular formula: $C_{10}H_{16}OSi$

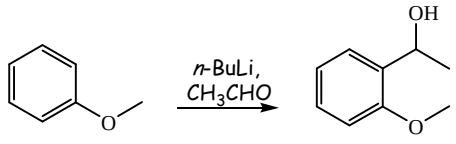
Molecular weight: 180.32 g/mol

Physical aspect: colourless liquid

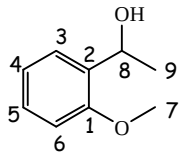
^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
0.32	s	-	9	8, 9, 10
3.85	s	-	3	7
6.88	d	8.2	1	6
7.00	dt	7.3, 0.8	1	4
7.34-7.47	m	-	2	3, 5

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
-0.97	8, 9, 10
54.98	7
109.48	6
120.38	4
127.90	2
130.70	5
134.94	3
164.33	1

IX. 4. 2. Preparation of 1-(2-methoxyphenyl)ethanol



Anisole (110 µl, 1 mmol, 1 eq.) was added to dry, freshly distilled THF (1 ml) in a dry, two-necked flask (10 ml), under argon. *n*-BuLi (625 µl, 1.6 M in hexane, 1 mmol, 1 eq.) was added dropwise at room temperature. The colour of the reaction mixture turned to yellow then orange. After six hours stirring, acetaldehyde (115 µl, 2 mmol, 2 eq.) was added dropwise. After 30 minutes stirring, water was added and the mixture was extracted by diethyl ether. The separated organic phase was dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash column chromatography using a 4 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.33) to obtain the title compound as a pure product (128 mg, *84%* yield).



Registry number: 13513-82-1

Molecular formula: $C_9H_{12}O_2$

Molecular weight: 152.19 g/mol

Physical aspect: colourless oil

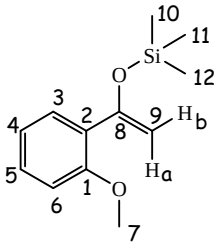
^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.49	d	6.5	3	9
2.74	s	-	1	OH
3.84	s	-	3	7
5.08	q	6.5	1	8
6.86	d	8.2	1	6
6.95	dt	7.5, 0.7	1	4
7.23	dt	7.9, 1.7	1	5
7.33	dd	7.5, 1.6	1	3

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
22.81	9
55.15	7
66.30	8
110.30	6
120.69	4
125.98	5
128.16	3
133.40	2
156.40	1

IX. 4. 3. Preparation of (1-(2-methoxyphenyl)vinyloxy)trimethylsilane

Dry, freshly distilled THF (2 ml) was placed in a two-necked, flame-dried flask (25 ml) under argon. It was cooled down to 0°C and diisopropylamine (180 µl, 1.25 mmol, 1.25 eq.) was added followed by *n*-BuLi (750 µl, 1.6 M in hexane, 1.20 mmol, 1.20 eq.). After 30 minutes stirring at 0°C, the mixture was cooled down to -78°C and the ketone (140 µl, 1 mmol, 1 eq.) was added dropwise. Directly after the addition, some solid (probably frozen ketone) was observed which disappeared in a few minutes. The temperature was kept between -78°C and -60°C during 1 hour, and then TMSCl (200 µl, 1.6 mmol, 1.6 eq.) was added dropwise. The mixture was let warm up slowly, during one hour, to -50°C, where the reaction was complete based on TLC. Aqueous solution of $NaHCO_3$ was added to the mixture at this temperature, and it was extracted by diethyl ether. The separated organic phase was dried over Na_2SO_4, filtered and evaporated. The NMR analysis of the obtained crude product showed complete conversion to the silylenol ether.

Using KHMDS as base gave similar results. Contrary to that, using NaH as base, the starting material was recovered.



Registry number: 135339-88-7

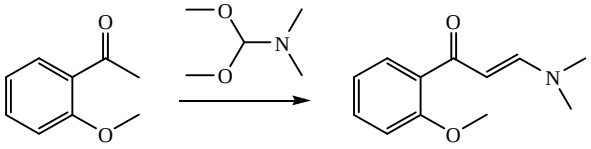
Molecular formula: $C_{12}H_{18}O_2Si$

Molecular weight: 222.36 g/mol

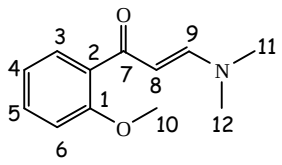
Physical aspect: colourless liquid

^{1}H-NMR (300 MHz, $CDCl_3$)					^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	Mult.	J (Hz)	Int.	N°	δ (ppm)	N°
0.08	s	-	9	10, 11, 12	0.23	10, 11, 12
3.70	s	-	3	7	55.31	7
4.51	s	-	1	9a, 9b	96.52	9
4.88	s	-	1		110.91	6
6.70-6.82	m	-	2	4, 6	120.05	4
					126.74	2
7.06-7.16	m	-	1	5	128.97, 129.04	3, 5
7.36	dd	7.7, 1.8	1	3	152.91	1
					156.91	8

IX. 4. 4. Preparation of 3-(dimethylamino)-1-(2-methoxyphenyl)prop -2-en-1-one



The mixture of 2-methoxy-acetophenone (420 µl, 3 mmol, 1 eq.) and *N*,*N*-dimethylformamide-dimethylacetal (820 µl, 6 mmol, 2 eq.) was refluxed at 110°C during 24 hours in a one-necked flask (5 ml) equipped with a condenser. Then it was concentrated on the vacuum pump and the residue was dissolved in DCM. It was washed with brine, dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using ethyl acetate as eluent (R_f = 0.18) to obtain the title compound as a pure product (610 mg, *99%* yield).



Registry number: 195813-59-3

Molecular formula: $C_{12}H_{15}NO_2$

Molecular weight: 205.25 g/mol

Physical aspect: yellow oil

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
2.91	bs	-	3	11, 12
3.03	bs	-	3	
3.85	s	-	3	10
5.55	d	12.7	1	8
6.88-7.02	m	-	2	4, 6
7.34	ddd	8.2, 7.6, 1.8	1	5
7.47	d	7.0	1	3
7.40-7.65	bm	-	1	9

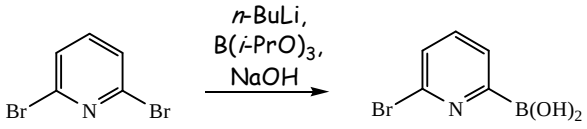
^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
36.98*	11, 12
44.62*	
55.51	10
97.85*	8
111.27	6
120.15	4
129.03	3
130.34	5
131.30	2
154.21*	9
156.61	1
190.62*	7

*broad signal

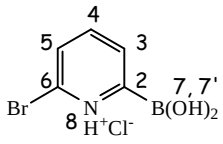
Infrared spectrum (film, cm^{-1}): 2999w, 2918w, 2837w, 2806w (C-H); 1635s (C=C); 1595m, 1577w, 1483m (aromatic C-C); 1537s (C=O); 1433w; 1417w; 1350s; 1276m, 1238m; 1105m; 1068m; 1041m; 1020m; 979w; 900m; 756s.

Mass spectrum (APCI) m/z (relative intensity): 206 $[M+H]^+$ (28%), 147 (M-58, $[C_9H_7O_2]^+$) (13%), 135 (M-70, $[C_8H_7O_2]^+$) (100%).

IX. 4. 5. Preparation of 6-bromopyridine-2-yl-2-boronic acid



n-BuLi (15 ml, 1.6 M, 24 mmol, 1.2 eq.) was added to dry, freshly distilled THF (30 ml), and the mixture was cooled to -78°C. Then 2,6-dibromopyridine (4.8 g, 20 mmol, 1.0 eq.) dissolved in THF (10 ml) was added dropwise. The colour of the reaction mixture turned to yellow, and later on, black. After 45 min stirring at -78°C, B(*i*-PrO)$_3$ (5.6 ml, 24 mmol, 1.2 eq) was added dropwise. The mixture was stirred at -78°C for additional 2 hours, and then, at room temperature during 1 hour. The reaction was quenched by the addition of 3% aqueous NaOH solution (200 ml). The resulting aqueous layer was cooled to 0°C and acidified to pH=5-6 with 3N HCl solution. The mixture was extracted with ethyl acetate, and the organic layer was concentrated. Diethyl ether was added to the obtained crude oil in order to precipitate the product. The formed precipitate was filtered off to obtain the required product in its protonated form (730 mg, *15%* yield).

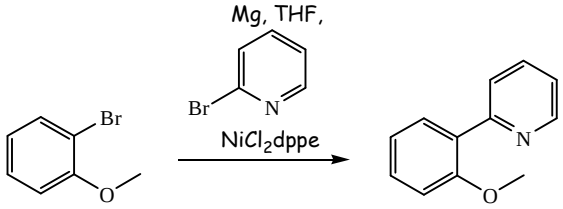


Molecular formula: $C_5H_5BBrNO_2xHCl$
Molecular weight: 238.27 g/mol
Physical aspect: white solid

^{1}H-NMR (300 MHz, d-DMSO)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
6.52	s	-	1	8*
7.62	dd	7.9, 1.2	1	3
7.70	t	7.5	1	4
7.78	dd	7.2, 1.2	1	5
8.43	s	-	2	7, 7’

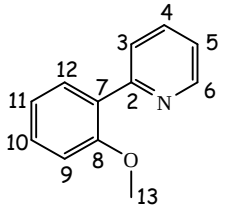
*coordinated proton

IX. 4. 6. Preparation of 2-(2-methoxyphenyl)pyridine



A mixture of *ortho*-bromoanisole (2.50 ml, 20 mmol, 1 eq.) and magnesium powder (486 mg, 20 mmol, 1 eq.) added to dry, freshly distilled THF (30 ml) was stirred during 2 hours in a dry, two-necked flask (25 ml), under argon. The magnesium powder disappeared and a grey solution was obtained. In a separated flask, a mixture of 2-bromopyridine (1.9 ml, 20 mmol, 1 eq.) and $NiCl_2$dppe (346 mg, 0.66 mmol, 3.3 mol%) in freshly distilled, dry THF (26 ml) was cooled down to 0°C. The Grignard was transferred into this mixture. The reaction was kept at 0°C during 30 minutes, then let warm up to room temperature and stirred overnight. It was quenched with saturated aqueous NH_4Cl solution and extracted with DCM. The organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 10 to 1 mixture of petrol ether and ethyl

acetate as eluent (R_f = 0.11) to obtain the title compound as a pure product (3.43 g, *93%* yield).



Registry number: 5957-89-1

Molecular formula: $C_{12}H_{11}NO$

Molecular weight: 185.22 g/mol

Physical aspect: colourless oil

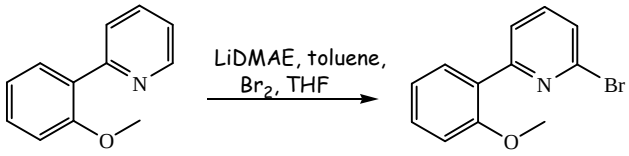
^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
3.85	s	-	3	13
7.00	d	8.3	1	9
7.08	dt	7.5, 1.0	1	10
7.19	ddd	7.4, 4.9, 1.2	1	5
7.37	ddd	8.3, 7.5, 1.8	1	11
7.69	dt	7.7, 1.8	1	4
7.76	dd	7.6, 1.8	1	3
7.81	td	8.0, 1.0	1	12
8.70	ddd	4.9, 1.7, 0.9	1	6

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
55.56	13
111.33	9
120.99	5
121.60	11
125.06	3
129.12	7
129.86	10
131.10	12
135.55	4
149.36	6
156.09	2
156.87	8

Infrared spectrum (film, cm^{-1}): 3055w, 2916w, 2833w (C-H); 1600w, 1583m, 1495m (aromatic C-C); 1462s; 1438w; 1423m; 1299w; 1257w; 1240m; 1122w; 1060w; 1024s; 792w; 754s.

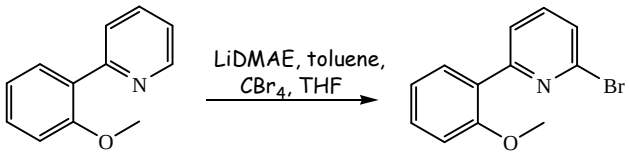
IX. 4. 7. Preparation of 2-bromo-6-(2-methoxyphenyl)pyridine

Procedure A:

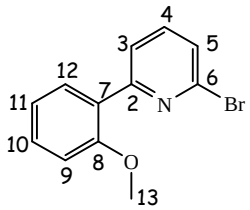


A solution of 2-dimethylaminoethanol (0.2 ml, 2 mmol, 1 eq.) in dry, freshly distilled toluene (2.5 ml) was cooled to 0°C and treated with *n*-BuLi (2.5 ml, 1.6M in hexane, 4 mmol, 2 eq.). The solution turned to yellow. After 30 minutes stirring at 0°C, the mixture was cooled down to -40°C and a solution of anisylpyridine (370 mg, 2 mmol, 1 eq.) in toluene (5 ml) was added dropwise. After 1 hour at -40°C, the dark orange mixture was cooled down to -78°C and a solution of bromine (0.2 ml, 4 mmol, 2 eq.) in freshly distilled, dry THF (5 ml) was added dropwise. A light grey solution was obtained, which turned to darker as the temperature was let increase to -10°C. Then it was quenched with 10% $Na_2S_2O_3$ aqueous solution. The mixture was extracted with diethyl ether, dried over $MgSO_4$, filtered and evaporated under vacuum. The resulted crude product was purified by flash column chromatography using DCM as eluent (R_f = 0.79) to obtain the title compound (180 mg) which was unfortunately not pure. Unreacted starting material was recovered and some butylated byproduct (*18%*) was also isolated.

Procedure B:



A solution of 2-dimethylaminoethanol (0.4 ml, 4 mmol, 2 eq.) in dry, freshly distilled toluene (5 ml) was cooled to 0°C and treated with *n*-BuLi (5 ml, 1.6 M in hexane, 8 mmol, 4 eq.). The solution turned to yellow. After 30 minutes stirring at 0°C, the mixture was cooled down to -40°C and a solution of anisylpyridine (370 mg, 2 mmol, 1 eq.) in toluene (5 ml) was added dropwise. After 1 hour at -40°C, the dark orange mixture was cooled down to -78°C and a solution of carbontetrabromide (1.66 g, 5 mmol, 2.5 eq.) in freshly distilled, dry THF (10 ml) was added dropwise. A light grey solution was obtained, which turned to darker as the temperature was allowed to increase. It was quenched with water as the temperature rose to -30°C. The mixture was extracted with diethyl ether, dried over $MgSO_4$, filtered and evaporated under vacuum. The resulted crude product was purified by flash column chromatography using a 15 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.23), then a second flash column chromatography was carried out using DCM as eluent (R_f = 0.79) to obtain the title compound (36 mg *7%* yield) and some butylated byproduct (132 mg, *27%*) in pure form.



Molecular formula: $C_{12}H_{10}BrNO$

Molecular weight: 264.12 g/mol

Physical aspect: brown liquid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
3.86	s	-	3	13
6.98	d	8.3	1	9
7.07	dt	7.6, 0.9	1	10
7.37	m	-	2	5, 11
7.54	t	7.8	1	4
7.85	dd	7.7, 1.0	2	3, 12

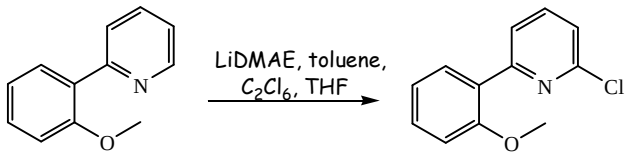
^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
55.56	13
111.33	9
121.09	11
123.89	3
125.87	5
127.10	7
130.57	10
131.32	12
138.07	4
141.29	6
156.88	2
156.99	8

Infrared spectrum (film, cm^{-1}): 3074w, 3001w, 2958w, 2935w, 2837w (C-H); 1600m, 1573m, 1546m, 1492m (aromatic C-C); 1463m; 1427s; 1390m; 1305w; 1259m; 1240m; 1161m; 1126s; 1031s; 981w; 813m; 798m; 752s.

Mass spectrum (APCI) m/z (relative intensity): 264 and 266 $[M+H]^+$ (78%), 249 and 251 (M-14, $[C_{11}H_7BrNO]^{\cdot +}$) (100%), 231 (M-32, $[C_{11}H_6BrN]^{\cdot +}$) (40%), 170 (M-93, $[C_{11}H_8NO]^+$) (20%).

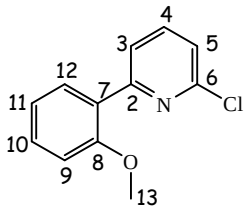
High resolution mass spectrum (ES+, $M+H^+$): for $C_{12}H_{11}NOBr$, ^{79}Br: calculated: 264.0024, found: 264.0032, ^{81}Br: found: 266.0013.

IX. 4. 8. Preparation of 2-chloro-6-(2-methoxyphenyl)pyridine



A solution of 2-dimethylaminoethanol (0.8 ml, 8 mmol, 4 eq.) in dry, freshly distilled toluene (10 ml) was cooled to 0°C and treated with *n*-BuLi (10 ml, 1.6M in hexane, 16 mmol, 8 eq.). The solution turned to yellow. After 30 minutes stirring at 0°C, the mixture was cooled down to -40°C and a solution of anisylpyridine (370 mg, 2 mmol, 1 eq.) in toluene (5 ml) was added dropwise. After 1 hour at -40°C, the dark orange mixture was cooled down to -78°C and a solution of hexachloroethane (1.5 g, 6.4 mmol, 3.2 eq.) in freshly distilled, dry THF (20 ml) was added very fast. A light purple solution was obtained, which turned to dark purple as the temperature was let increase to room temperature. Then, it was cooled back to 0°C and quenched with water. The mixture was extracted with diethyl ether, dried over $MgSO_4$, and evaporated under vacuum. The resulted crude product was purified by flash column chromatography using DCM as eluent (R_f = 0.89) to obtain the title compound (154 mg, *35%* yield) and some butylated byproduct (163 mg, *34%*) in pure form.

When the lithiated poduct was added dropwise into the solution of the hexachloroethane (inverse addition), we obtained the title compound in somewhat higher yield (176 mg, *40%* yield), and the amount of the butylated byproduct decreased (114 mg, *24%).*



Registry number: 851595-25-0

Molecular formula: $C_{12}H_{10}ClNO$

Molecular weight: 219.67 g/mol

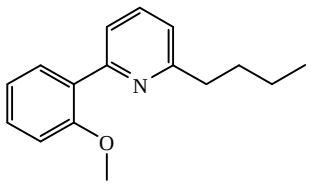
Physical aspect: colourless oil

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
3.86	s	-	3	13
6.99	d	8.3	1	9
7.08	t	7.5	1	10
7.23	d	7.8	1	5
7.38	dt	7.6, 1.3	1	11
7.64	dt	7.8, 0.5	1	4
7.81	d	7.8	1	3
7.85	dd	7.7, 1.7	1	12

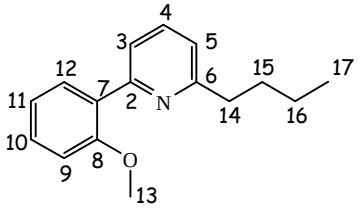
^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
55.50	13
111.34	9
121.03	5
121.95	11
123.44	3
127.30	7
130.44	10
131.20	12
138.22	4
150.65	6
156.39	2
157.00	8

Infrared spectrum (film, cm^{-1}): 3095w, 3074w, 2830w (C-H); 1600m, 1573m, 1552m, 1492m (aromatic C-C); 1463m; 1427m; 1392m; 1261m; 1240m; 1161m; 1135m; 1037w; 1022m; 821m; 800m; 748s.

Byproduct: ***2-butyl-6-(2-methoxyphenyl)pyridine***



This byproduct was purified by two subsequent flash column chromatographies using a 9 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.38) for the first one, and DCM as eluent (R_f = 0.69) for the second one.



Molecular formula: $C_{16}H_{19}NO$

Molecular weight: 241.15 g/mol

Physical aspect: brown liquid

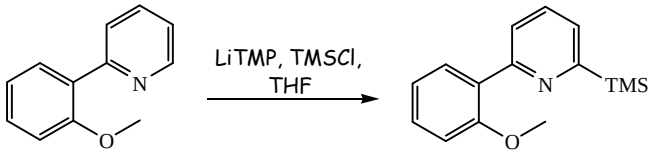
^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
0.96	t	7.4	3	17
1.37-1.47	m	-	2	16
1.72-1.82	m	-	2	15
2.87	t	7.9	2	14
3.84	s	-	3	13
6.99	d	8.3	1	9
7.04-7.11	m	-	2	5, 11
7.32-7.38	m	-	1	10
7.55-7.65	m	-	2	3, 4
7.76	dd	7.6, 1.7	1	12

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
13.97	17
22.49	16
32.13	15
38.13	14
55.54	13
111.31	9
120.54	5
121.02	11
122.20	3
129.30	7
129.66	10
131.23	12
135.88	4
155.15	2
156.89	8
161.96	6

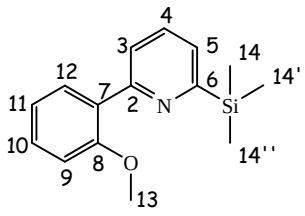
Infrared spectrum (film, cm^{-1}): 2955w, 2929w, 2858w (C-H); 1598w, 1571m, 1492m (aromatic C-C); 1463m; 1446m; 1242s (C-O); 1161w; 1024m; 752s.

Mass spectrum (APCI) m/z (relative intensity): 242 $[M+H]^+$ (100%), 227 (M-14, $[C_{15}H_{17}NO]^{\cdot +}$) (9%), 185 (M-56, $[C_{12}H_{11}NO]^{\cdot +}$) (21%).
High resolution mass spectrum (ES+, $M+H^+$): for $C_{16}H_{20}ON$, calculated: 242.1545, found: 242.1547.

IX. 4. 9. Preparation of 2-(2-methoxyphenyl)-6-(trimethylsilyl)pyridine



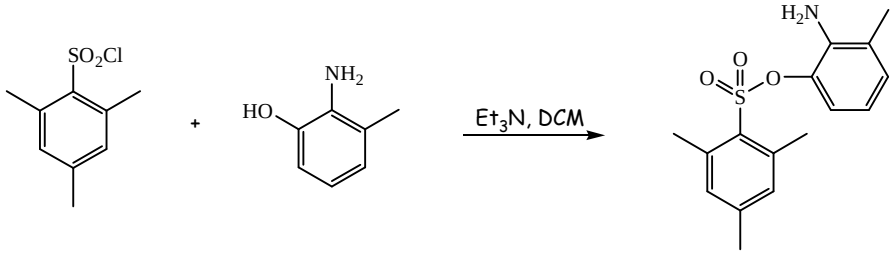
A solution of 2,2,6,6-tetramethylpiperidine (0.61 ml, 3.6 mmol, 3.3 eq.) in dry, freshly distilled THF (2 ml) was cooled down to 0°C and treated dropwise with *n*-BuLi (2.13 ml, 1.6M in hexane, 3.4 mmol, 3.1 eq.). After 30 min stirring, this solution was added dropwise, at 0°C, into the mixture of anisylpyridine (204 mg, 1.1 mmol, 1 eq.) and distilled TMSCl (0.43 ml, 3.4 mmol, 3.1 eq.) in THF (3 ml). The reaction was stirred during 2 hours at 0°C, and then hydrolyzed by water. It was extracted by DCM, dried over Na_2SO_4, filtered and evaporated. Total conversion was observed by NMR. Unfortunately the crude product could not be purified by column chromatography due to degradation.



Registry number: 634591-10-9
Molecular formula: $C_{15}H_{19}NOSi$
Molecular weight: 257.40 g/mol
Physical aspect: colourless liquid

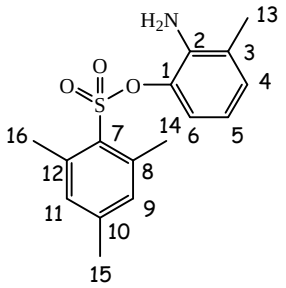
^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
0.35	s	-	9	14, 14', 14"
3.87	s	-	3	13
7.00	d	8.3	1	9
7.09	dt	7.5, 1.0	1	11
7.31-7.44	m	-	2	5, 10
7.58	t	7.7	1	4
7.79	dd	8.1, 1.1	1	3
7.93	dd	7.7, 1.8	1	12

IX. 4. 10. Preparation of 2-amino-3-methylphenyl 2,4,6-trimethyl-benzenesulfonate



2-Amino-3-methylphenol (1.24 g, 10 mmol, 1 eq.) was dissolved in DCM (25 ml) in a one-necked flask (100 ml). Triethylamine (1.39 ml, 10 mmol, 1 eq.) was added to the solution. Then the mixture was cooled down to 0°C and mesitylenesulfonyl chloride (2.20 g, 10 mmol, 1 eq.) was added to it. The reaction mixture was let warm up to room temperature. After 1 hour of stirring at room temperature the reaction was complete, based on TLC. Water was added and the separated organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated. The red-brown crude product was purified by flash column chromatography using a 4 to 1

mixture of petrol ether and ethyl acetate as eluent (R_f = 0.45) to obtain the title compound as a pure product (2.72 g, *89%* yield).



Registry number: 278179-93-4

Molecular formula: $C_{16}H_{19}NO_3S$

Molecular weight: 305.39 g/mol

Physical aspect: light brown solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
2.18	s	-	3	13
2.35	s	-	3	15
2.56	s	-	6	14, 16
3.85	bs	-	2	NH_2
6.31	d	7.9	1	6
6.44	t	7.8	1	5
6.91	d	7.5	1	4
7.00	s	-	2	9, 11

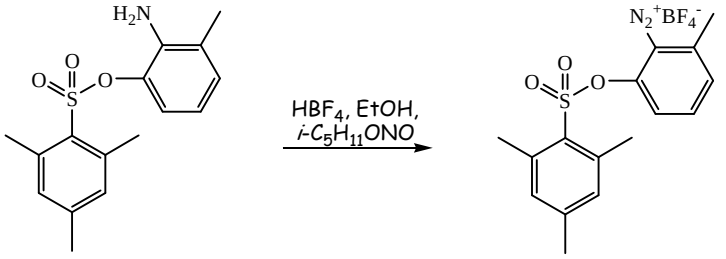
^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
17.45	13
21.12	15
22.76	14, 16
117.20	6
119.39	5
128.60	4
131.80	9, 11
140.34	8, 12
124.68, 131.17, 136.73, 138.50, 143.86	1, 2, 3, 7, 10

Infrared spectrum (film, cm^{-1}): 3483w, 3396w (N-H); 2939w, 2856w (C-H); 1625m, 1600m (NH_2); 1483m (aromatic C-C); 1444w; 1361s, 1190s, 1176s (S=O); 1153w; 1124w; 1056w; 916s (S-O); 854w; 783m, 759m.

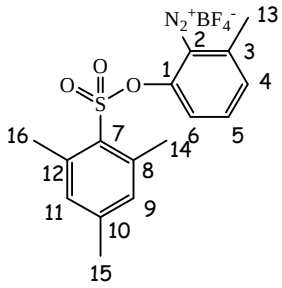
Mass spectrum (APCI) m/z (relative intensity): 306 $[M+H]^+$ (100%), 123 (M-182, $[C_7H_9NO]^{\cdot +}$) (24%).

Melting point: 121-124°C

IX. 4. 11. Preparation of 2-diazo-3-methylphenyl (2,4,6-trimethyl-benzenesulfonate) tetrafluoroborate



Ethanol (20 ml) was placed in a one-necked flask (100 ml). It was cooled down to 0°C and HBF_4 (1.70 ml, 54% in ether, 12 mmol, 3 eq.) was added to it followed by the sulfonate (1.22 g, 4 mmol, 1 eq.). The resulted dark brown mixture was treated dropwise by isoamyl nitrite (875 µl, 6.8 mmol, 1.7 eq.). In a few minutes, considerable amount of yellow precipitate formed. Diethyl ether (10 ml) was added to dilute the mixture and it was stirred for an additional 1 hour at 0°C. Then the precipitate was filtered off and washed with cold water and diethyl ether several times. The water content of the resulted product can be eliminated by freeze-drying, but this long process is unnecessary for the next step of the synthesis. Global yield will be given for the two steps.



Registry number: 278179-64-9

Molecular formula: $C_{16}H_{17}SO_3N_2^+BF_4^-$

Molecular weight: 404.19 g/mol

Physical aspect: light yellow solid

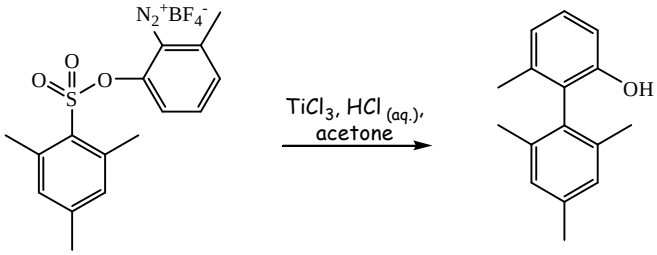
^{1}H-NMR (300 MHz, Acetone-d^{6})				
δ (ppm)	Mult.	J (Hz)	Int.	N°
2.39	s	-	3	15
2.65	s	-	6	14, 16
2.96	s	-	3	13
7.28	s	-	2	9, 11
7.40	d	8.5	1	6
7.86	d	8.0	1	4
8.25	t	8.3	1	5

^{13}C-NMR (75 MHz, Acetone-d^{6})	
δ (ppm)	N°
20.16	13
22.19	15
23.75	14, 16
111.54	2
123.22	6
132.60	4
134.45	9, 11
142.86	5
145.15	8, 12
130.43, 148.63, 149.92	3, 7, 10
151.64	1

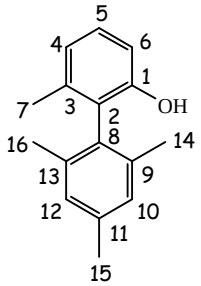
Infrared spectrum (film, cm^{-1}): 2930w (C-H); 2268m (N_2^+); 1600m; 1569m; 1479m (aromatic C-C); 1380s, 1191s, 1178s (S=O); 1058s; 1033m; 960m; 815w; 794m.

Mass spectrum (APCI) m/z (relative intensity): M' = M-BF_4^-, 318 $[M'+H]^{\cdot +}$ (13%), 253 (M'-64, $[C_{16}H_{17}N_2O]^+$) (10%), 183 (M'-134, $[C_9H_{11}O_2S]^+$) (35%), 167 (M'-150, $[C_9H_{11}OS]^+$) (29%), 134 (M'-183, $[C_7H_6N_2O]^{\cdot +}$) (100%), 119 (M'-198, $[C_9H_{11}]^+$) (88%).

IX. 4. 12. Preparation of 1-hydroxy-3-methyl-2-(2,4,6-trimethylphenyl)benzene



The crude product of the previous reaction was dissolved in acetone (8 ml) in a one-necked flask (50 ml) at 0°C. The solution was treated dropwise with $TiCl_3$ (3.12 ml, 30 w/w% in 2 N HCl; 8 mmol, 2 eq.). The dark blue colour of the $TiCl_3$ solution disappeared on the addition and gas evolution was observed. The formed gases were evacuated from the flask through a needle. After the addition of the total amount of $TiCl_3$ the dark blue colour stayed and the gas evolution was ceased in 30 minutes. The mixture was diluted with water and extracted with DCM. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated. The brown crude product was purified by flash column chromatography using a 40 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.14) to obtain the title compound as a pure product (650 mg, *72%* yield over the 2 steps).



Registry number: 278179-81-0

Molecular formula: $C_{16}H_{18}O$

Molecular weight: 226.31 g/mol

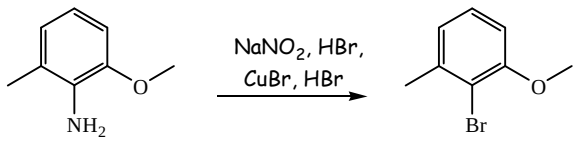
Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.92	s	-	3	7
1.95	s	-	6	14, 16
2.34	s	-	3	15
4.50	s	-	1	OH
6.84	t	7.4	2	4, 6
6.99	s	-	2	10, 12
7.17	t	7.8	1	5

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
19.48	7
19.71	14, 16
21.11	15
112.22	6
121.89	4
128.26	5
128.92	10, 12
137.65	9, 13
126.05, 130.27, 137.05, 138.01	2, 3, 8, 11
152.31	1

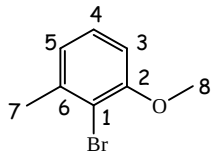
Infrared spectrum (film, cm^{-1}): 3530bs (OH); 2970w, 2920w (C-H); 1608w, 1573m, 1460s (aromatic C-C); 1377w; 1326w; 1276m; 1253m; 1178s (C-O); 1083w; 1033w; 1004w; 948w; 850s; 781s, 746s.
Mass spectrum (APCI) m/z (relative intensity): 227 $[M+H]^+$ (100%), 212 (M-14, $[C_{15}H_{16}O]^{\cdot +}$) (19%), 194 (M-32, $[C_{15}H_{14}]^{\cdot +)}$ (25%).
Melting point: 58-60°C

IX. 4. 13. Preparation of 2-bromo-1-methoxy-3-methylbenzene



The substrate (4.12 g, 30 mmol, 1 eq.) was added to an aqueous solution of HBr (27 ml, 48 w/w% in water) at 0°C in a two-necked flask (150 ml). After a few minutes stirring, a cold solution of $NaNO_2$ (2 g, 30 mmol, 1 eq.) in water (42 ml) was added dropwise. 30 minutes later, it was transferred into the solution of CuBr (6.06 g, 42

mmol, 1.4 eq.) in aqueous HBr (27 ml, 48 w/w% in water). Then water was added (54 ml) and the mixture was heated to 130°C for 2 hours. It was cooled down, diluted with ethyl acetate and water and the layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic phases were washed with 1 M HCl and brine, dried over Na_2SO_4, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 40 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.44) to obtain the title compound as a pure product (4.74 g, *78%* yield).



Molecular formula: C_8H_9BrO
Molecular weight: 201.06 g/mol
Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
2.41	s	-	3	7
3.88	s	-	3	8
6.74	d	8.2	1	3
6.86	d	7.6	1	5
7.15	t	7.9	1	4

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
23.25	7
56.26	8
109.11	3
114.17	1
122.90	5
127.44	4
139.67	6
155.93	2

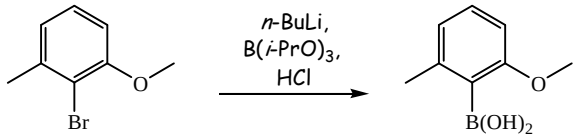
Infrared spectrum (film, cm^{-1}): 2925m, 2854w (C-H); 1593w, 1569m (aromatic C-C); 1469s; 1298m; 1265s(C-O); 1082s(C-O); 1029m; 800w; 765m.

Mass spectrum (APCI) m/z (relative intensity): 203 and 201 $[M+H]^+$ (100%), 122 (M-78, $[C_8H_{10}O]^{\cdot +}$) (10%).

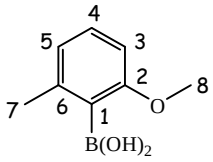
Melting point: 35-38°C

Elementary analysis: calculated: C: 47.79%, H: 4.51%; found: C: 47.85%, H: 4.34%.

IX. 4. 14. Preparation of 2-methoxy-6-methylphenylboronic acid



The bromide (1.51 g, 7.5 mmol, 1 eq.) was dissolved in dry, distilled THF (19 ml) in a two-necked flask (100 ml) under argon. It was cooled down to -78°C and *n*-BuLi (3.6 ml, 2.5 M in hexane, 9 mmol, 1.2 eq.) was added dropwise. After 1 hour stirring at -78°C, B(*i*-PrO)$_3$ (7 ml, 30 mmol, 4 eq.) was added. After an additional 1 hour stirring at -78°C, the mixture was let warm up to room temperature and stirred overnight. Then water (2 ml) was added followed by the slow addition (during 1 hour) of a 2 M aqueous HCl solution (10 ml). Ethyl acetate was added and the layers were separated. The organic phase was extracted three times with 1 M aqueous solution of NaOH. The aqueous layers were combined and the pH was adjusted to 5. Then it was extracted with ethyl acetate. The organic layers were combined and evaporated to obtain, after drying on the vacuum pump, the title compound as a pure product (400 mg, *32%* yield).



Molecular formula: $C_8H_{11}BO_3$

Molecular weight: 165.98 g/mol

Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
2.56	s	-	3	7
3.87	s	-	3	8
6.42	bs	-	2	OH
6.75	d	8.3	1	3
6.86	d	7.5	1	5
7.27	t	7.8	1	4

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
23.30	7
55.69	8
107.54	3
124.23	5
131.18	4
146.97	6
164.51	2

C-1 cannot be seen due to sign broadening

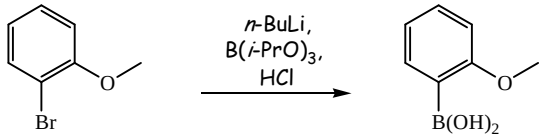
Infrared spectrum (film, cm^{-1}): 3307bs (O-H); 2921w, 2852w (C-H); 1596w, 1571m (aromatic C-C); 1463s; 1433m; 1336s (B-O); 1288w; 1249s(C-O); 1087s (C-O); 1008m; 829m; 779s; 740w.

Mass spectrum (CI) m/z (relative intensity): 167 $[M+H]^+$ (100%), 166 (M, $[C_8H_{11}BO_3]^{\cdot +}$) (60%), 149 (M-17, $[C_8H_{10}BO_2]^+$) (20%), 123 (M-43, $[C_8H_{11}O]^+$) (40%).

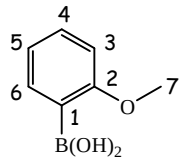
Melting point: 108-111°C

High resolution mass spectrum (EI+, $M^{\cdot +}$): for $C_8H_{11}BO_3$, calculated: 166.0801, found: 166.0805.

IX. 4. 15. Preparation of 2-methylphenylboronic acid



The bromide (2.5 g, 13.4 mmol, 1 eq.) was dissolved in dry, distilled THF (50 ml) in a two-necked flask (250 ml) under argon. It was cooled down to -78°C and *n*-BuLi (10 ml, 1.6 M in hexane, 16 mmol, 1.2 eq.) was added dropwise. After 15 minutes stirring at -78°C, B(*i*-PrO)$_3$ (6.2 ml, 26.7 mmol, 2 eq.) was added. After an additional 1 hour stirring at -78°C, the mixture was let warm up to room temperature for 1 hour. The solvents were evaporated and the oil residue was poured onto a 1 to 1 mixture of ice and water. It was acidified with aqueous HCl to pH 5-6 and extracted with diethyl ether. The organic layer was dried over $MgSO_4$, filtered and evaporated to obtain the crude product (2.12 g). After re-crystallization from benzene, the title compound was obtained as a pure product (1.2 g, *59%* yield).



Registry number: 5720-06-9

Molecular formula: $C_7H_9BO_3$

Molecular weight: 151.96 g/mol

Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
3.90	s	-	3	7
6.64	bs	-	2	OH
6.91	d	8.3	1	3
7.03	dt	7.3, 0.5	1	5
7.40-7.50	m	-	1	4
7.87	dd	7.3, 1.8	1	6

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
55.42	7
109.92	3
121.21	5
132.80	4
136.83	6
164.46	2

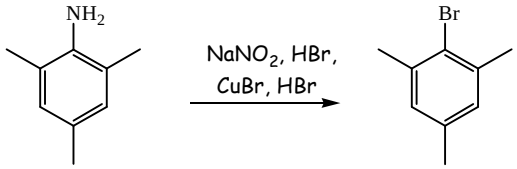
C-1 cannot be seen due to sign broadening

Infrared spectrum (film, cm^{-1}): 3361bs (O-H); 3072w, 3008w, 2947w, 2842w (C-H); 1598s, 1573w (aromatic C-C); 1485s; 1454m; 1434m; 1398m; 1342s (B-O); 1228s (C-O); 1163s (C-O); 1097m; 1053s; 1024s; 954w; 858w.

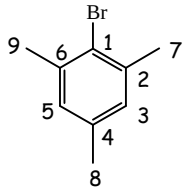
Mass spectrum (CI) m/z (relative intensity): 153 $[M+H]^+$ (100%), 152 (M, $[C_7H_9BO_3]^{\cdot +}$) (29%), 109 (M-43, $[C_7H_9O]^+$) (14%).

Melting point: 89-92°C

IX. 4. 16. Preparation of 2-bromo-1,3,5-trimethylbenzene



The substrate (1.4 ml, 10 mmol, 1 eq.) was added to an aqueous solution of HBr (9 ml, 48 w/w% in water) at 0°C in a two-necked flask (50 ml). After a few minutes stirring, a cold solution of $NaNO_2$ (690 mg, 10 mmol, 1 eq.) in water (14 ml) was added dropwise. 30 minutes later, it was transferred into the solution of CuBr (2.02 g, 14 mmol, 1.4 eq.) in aqueous HBr (9 ml, 48 w/w% in water). Then, water (18 ml) was added and the mixture was heated to 130°C for 2 hours. It was cooled down, diluted with ethyl acetate and water and the layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic phases were washed with 1 M HCl and brine, dried over Na_2SO_4, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 9 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.84) to obtain the title compound as a pure product (1.0 g, *51%* yield).



Registry number: 576-83-0

Molecular formula: $C_9H_{11}Br$

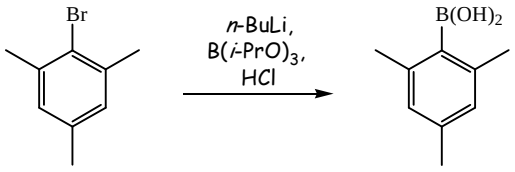
Molecular weight: 199.09 g/mol

Physical aspect: colourless liquid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
2.19	s	-	3	8
2.33	s	-	6	7, 9
6.83	s	-	2	3, 5

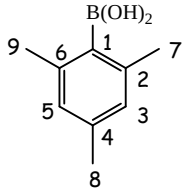
^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
20.68	8
23.71	7, 9
124.08	1
128.88	3, 5
136.04	4
137.67	2, 6

IX. 4. 17. Preparation of 2,4,6-trimethylphenylboronic acid



The bromide (1.5 ml, 10 mmol, 1 eq.) was dissolved in dry, distilled THF (25 ml) in a two-necked flask (100 ml) under argon. It was cooled down to -78°C and *n*-BuLi (4.8 ml, 2.5 M in hexane, 12 mmol, 1.2 eq.) was added dropwise. After 1 hour stirring at -78°C, B(*i*-PrO)$_3$ (9.4 ml, 40 mmol, 4 eq.) was added. After an additional 1 hour stirring at -78°C, the mixture was let warm up to room temperature and stirred overnight. It was cooled to 0°C and 1 M aqueous HCl solution (17 ml) was added. The mixture was stirred during 2 hours at room temperature. Then it was extracted with diethyl

ether. The organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated to obtain the crude product (2.2 g). After re-crystallization from benzene, the title compound was obtained as a pure product (1.1 g, *67%* yield).



Registry number: 5980-97-2

Molecular formula: $C_9H_{13}BO_2$

Molecular weight: 164.01 g/mol

Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
2.25	s	-	3	8
2.32	s	-	6	7, 9
4.88	s	-	2	OH
6.81	s	-	2	3, 5

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
21.10	8
22.00	7, 9
127.24	3, 5
138.63	4
139.62	2, 6

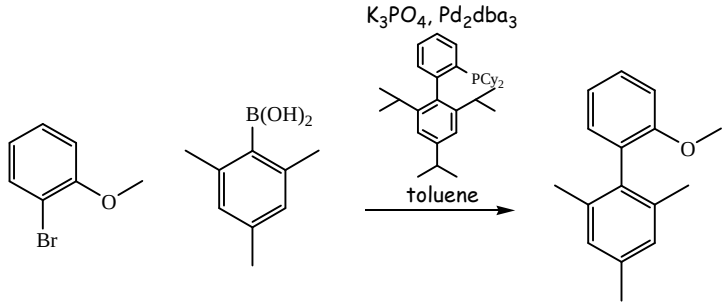
C-1 cannot be seen due to sign broadening

Infrared spectrum (film, cm^{-1}): 3307bs (O-H); 2972w, 2916w (C-H); 1610m, 1560w (aromatic C-C); 1436m; 1338s (B-O); 1164w; 1101s; 1014s; 844w; 827w.

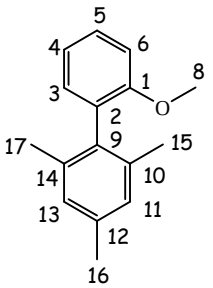
Mass spectrum (CI) m/z (relative intensity): 165 $[M+H]^+$ (71%), 147 (M-17, $[C_9H_{12}BO]^+$) (26%), 121 (M-43, $[C_9H_{13}]^+$) (100%).

Melting point: 94-97°C

IX. 4. 18. Preparation of 1-methoxy-2-(2,4,6-trimethylphenyl)benzene



The boronic acid (164 mg, 1 mmol, 2 eq.), dry K_3PO_4 (318 mg, 1.5 mmol, 3 eq.), Pd_2dba_3 (18.3 mg, 0.02 mmol, 4 mol %) and X-Phos ligand (18.6 mg, 0.04 mmol, 8 mol %) were placed in a flame-dried Schlenk tube under argon. It was vacuumed and argon-filled three times. Then the bromide (62 µl, 0.5 mmol, 1 eq.) and dry, distilled and degassed toluene (1 ml) were added. The mixture was heated at 110°C during 24 hours. The original purple colour of the reaction turned to dark green. Ethyl acetate was added, and then the mixture was filtered on celite and evaporated. The resulted crude product was purified by flash column chromatography using a 40 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.22) to obtain the title compound as a pure product (57 mg, *50%* yield).



Registry number: 56692-73-0

Molecular formula: $C_{16}H_{18}O$

Molecular weight: 226.31 g/mol

Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.98	s	-	6	15, 17
2.32	s	-	3	16
3.73	s	-	3	8
6.09-7.06	m	-	5	4, 5, 6 11, 13
7.26-7.38	m	-	1	3

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
20.33	15, 17
21.12	16
55.38	8
110.75	6
120.58	4
127.88	11, 13
128.24	5
130.92	3
136.44	10, 14
129.44, 135.24, 136.48	2, 9, 12
156.66	1

Infrared spectrum (film, cm^{-1}): 2948w, 2916w (C-H); 1598w, 1577w (aromatic C-C); 1477w; 1454w; 1434w; 1255m; 1234m; 1116m; 1051w; 1027m; 1002w; 848m; 794w; 750s.

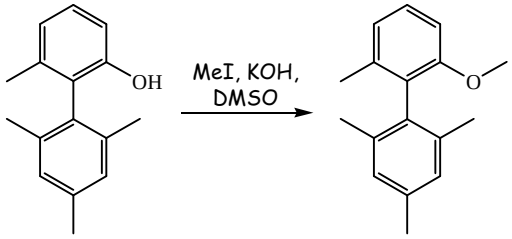
Mass spectrum (APCI) m/z (relative intensity): 227 $[M+H]^+$ (100%), 212 (M-14, $[C_{15}H_{16}O]^{\cdot +}$) (19%).

Melting point: 54-56°C

High resolution mass spectrum (ES+, $M+H^+$): for $C_{16}H_{19}O$, calculated: 227.1436, found: 227.1442.

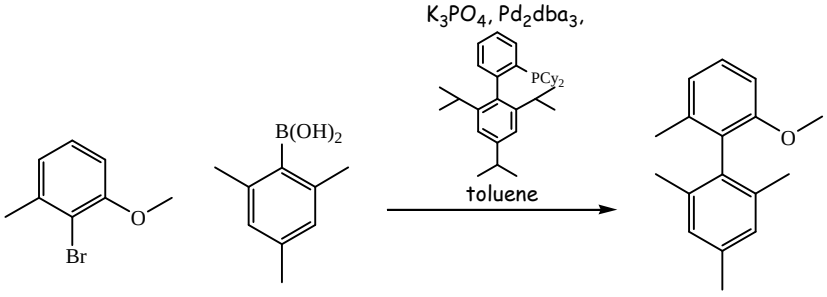
IX. 4. 19. Preparation of 1-methoxy-3-methyl-2-(2,4,6-trimethylphenyl)benzene

Procedure A:



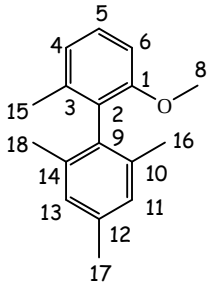
The hydroxy biphenyl (452 mg, 2 mmol, 1 eq.) was dissolved in DMSO (4 ml), and KOH (449 mg, 8 mmol, 4 eq.) was added to it. The colourless solution turned to yellow on the addition. MeI (190 µl, 3 mmol, 1.5 eq.) was added dropwise to the mixture and it was stirred overnight at room temperature. Then water was added and the mixture was extracted with DCM. The organic layer was washed with water, dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 15 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.45) to obtain the title compound as a pure product (460 mg, *96%* yield).

Procedure B:



The boronic acid (164 mg, 1 mmol, 2 eq.), the bromide (101 mg, 0.5 mmol, 1 eq.), dry K_3PO_4 (318 mg, 1.5 mmol, 3 eq.), Pd_2dba_3 (18.3 mg, 0.02 mmol, 4 mol %) and X-Phos ligand (18.6 mg, 0.04

mmol, 8 mol %) were placed in a flame-dried Schlenk tube under argon. It was vacuumed and argon-filled three times. Then dry, distilled and degassed toluene (1 ml) was added. The mixture was heated at 110°C during 24 hours. The original purple colour of the reaction turned to dark green. Ethyl acetate was added, and then the mixture was filtered on celite and evaporated. The resulted crude product was purified by flash column chromatography using a 15 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.45) to obtain the title compound as a pure product (15 mg, *13%* yield).



Molecular formula: $C_{17}H_{20}O$

Molecular weight: 240.34 g/mol

Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.90	s	-	9	15, 16, 18
2.32	s	-	3	17
3.68	s	-	3	8
6.81	d	8.2	1	6
6.89	d	7.6	1	4
6.93	s	-	2	11, 13
7.22	t	7.9	1	5

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
19.45	15
19.83	16, 18
21.18	17
55.56	8
108.05	6
122.29	4
127.63	5
127.97	11, 13
135.99	10, 14
128.98, 134.07, 136.19, 137.49	2, 3, 9, 12
156.66	1

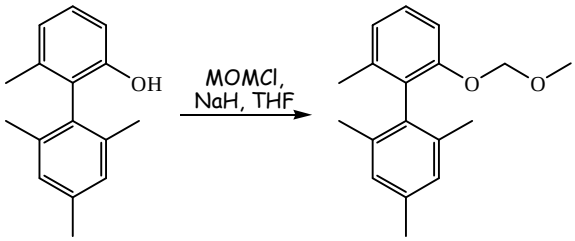
Infrared spectrum (film, cm^{-1}): 2943w, 2918w (C-H); 1596w, 1577m (aromatic C-C); 1465s; 1438w; 1292w; 1251s, 1083s (C-O); 1004w; 848m; 777m; 746m.

Mass spectrum (APCI) m/z (relative intensity): 241 $[M+H]^+$ (100%), 226 (M-14, $[C_{16}H_{18}O]^{\cdot +}$) (33%), 211 (M-29, $[C_{15}H_{15}O]^{+)}$ (10%), 194 (M-46, $[C_{15}H_{14}]^{\cdot +)}$ (10%).

Melting point: 57-60°C

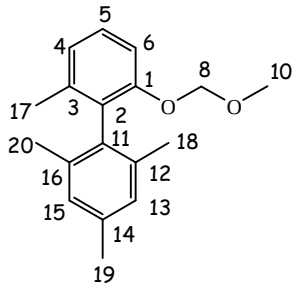
Elementary analysis: calculated: C: 84.96%, H: 8.39%; found: C: 84.72%, H: 8.38%.

IX. 4. 20. Preparation of 1-methoxymethoxy-3-methyl-2-(2,4,6-trimethylphenyl)benzene



NaH (120 mg, 60 w/w%, 2.97 mmol, 1.1 eq.) was suspended in dry, distilled THF (5.4 ml) in a dry, two-necked flask under argon. It was cooled down to 0°C and 2-(2,4,6-trimethylphenyl)-3-methyl phenol (610 mg, 2.7 mmol, 1 eq.) was added. After 45 minutes stirring at 0°C, methoxymethyl chloride (230 µl, 2.97 mmol, 1.1 eq.) was added dropwise. The ice bath was removed. After 1 hour stirring at room temperature, the reaction was complete. Water was added to the mixture and it was extracted with diethyl ether. The organic layer was dried over Na_2SO_4, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 20 to 1

mixture of petrol ether and ethyl acetate as eluent (R_f = 0.51) to obtain the title compound as a pure product (666 mg, *91%* yield).



Molecular formula: $C_{18}H_{22}O_2$

Molecular weight: 270.37 g/mol

Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.88	s	-	3	17
1.92	s	-	6	18, 20
2.32	s	-	3	19
3.28	s	-	3	10
5.03	s	-	2	8
6.93	s	-	2	13, 15
6.94	d	-*	1	6
7.04	d	7.5	1	4
7.20	t	8.1	1	5

*Due to an extensive overlap with the singlet at δ=6.93, this coupling constant could not be accurately measured.

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
19.60	17
19.95	18, 20
21.22	19
55.62	10
94.10	8
111.88	6
123.40	4
127.64	5
127.84	13, 15
129.84, 134.00, 136.09, 137.56	2, 3, 11, 14
135.83	12, 16
154.07	1

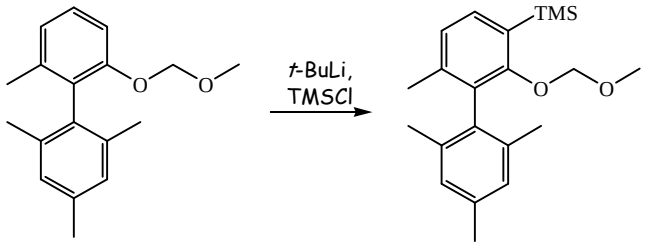
Infrared spectrum (film, cm^{-1}): 2950w, 2920w (C-H); 1577w (aromatic C-C); 1463m; 1244m; 1153s, 1047s (C-O); 989w; 923w; 850w; 781w; 740s.

Mass spectrum (APCI) m/z (relative intensity): 271 $[M+H]^+$ (1%), 239 (M-31, $[C_{17}H_{19}O]^+$) (100%), 224 (M-46, $[C_{16}H_{16}O]^{\cdot +}$) (22%), 209 (M-61, $[C_{16}H_{17}]^+$) (8%).

Melting point: 58-60°C

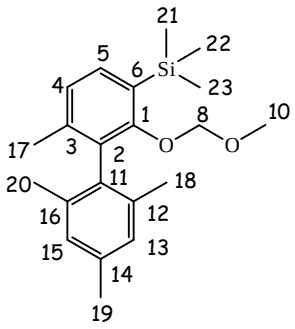
Elementary analysis: calculated: C: 79.86%, H: 8.19%; found: C: 79.59%, H: 8.18%.

IX. 4. 21. Preparation of (2-methoxymethoxy-4-methyl-3-(2,4,6-trimethylphenyl)phenyl)trimethylsilane



The substrate (135 mg, 0.5 mmol, 1 eq.) was dissolved in dry, freshly distilled THF (2.5 ml) in a dry, two-necked flask (25 ml), under argon. It was cooled down to -78°C and *t*-BuLi (590 µl, 1.7 M in pentane, 1 mmol, 2 eq.) was added dropwise. The colourless mixture turned to bright yellow from the first drop of *t*-BuLi. After 40 minutes stirring at -78°C, it was let warm up to room temperature. At this temperature the mixture became blurry. After 30 minutes, it was cooled back to 0°C and TMSCl (130 µl, 1 mmol, 2 eq.) was added dropwise. By the addition a white blurry mixture was obtained. The cooling bath was removed and stirring was continued at room temperature during 30 minutes. Aqueous, saturated solution of $NaHCO_3$ was added and the mixture was extracted by diethyl ether. The separated organic phase was dried over Na_2SO_4, filtered and evaporated. The NMR analysis of the obtained crude product (178 mg) showed complete conversion to the required silylated compound.

Carrying out the reaction using 1.25 eq *n*-BuLi, the product was obtained in *78%* yield.



Molecular formula: $C_{21}H_{30}O_2Si$

Molecular weight: 342.55 g/mol

Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
0.30	s	-	9	21, 22, 23
1.93	s	-	3	17
1.97	s	-	6	18, 20
2.31	s	-	3	19
2.95	s	-	3	10
4.44	s	-	2	8
6.92	s	-	2	13, 15
7.06	d	7.5	1	4
7.33	d	7.4	1	5

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
-0.32	21, 22, 23
19.66	17
20.14	18, 20
21.07	19
56.37	10
97.81	8
125.54	4
128.08	13, 15
134.05	5
136.54	12, 16
130.29, 132.79, 134.42, 136.59, 139.74	2, 3, 6, 11, 14
159.18	1

Infrared spectrum (film, cm^{-1}): 2952w, 2920w (C-H); 1585w; 1458w; 1436w; 1367m; 1245m; 1161m (C-O); 1047w; 1020w; 981m; 852s; 838s.

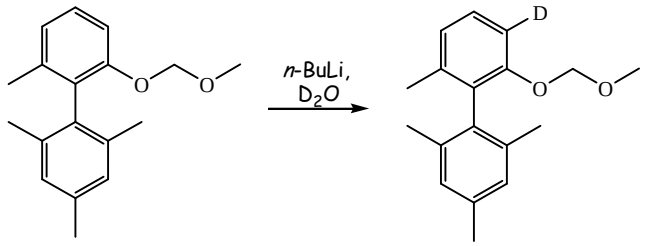
Mass spectrum (APCI) m/z (relative intensity): 343 $[M+H]^+$ (1%), 311 (M-31, $[C_{20}H_{27}OSi]^+$) (70%), 296 (M-46, $[C_{19}H_{24}OSi]^{\cdot +}$(53%),

281 (M-61, $[C_{19}H_{25}Si]^+$(37%), 239 (M-103, $[C_{17}H_{19}O]^+$(100%), 224 (M-118, $[C_{16}H_{16}O]^{\cdot +}$(33%), 209 (M-133, $[C_{16}H_{17}]^+$(31%).

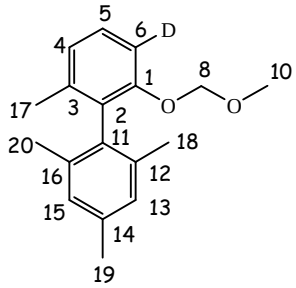
Melting point: 34-35°C

High resolution mass spectrum (ES+, M+Na): for $C_{21}H_{30}O_2NaSi$, calculated: 365.1913, found: 365.1916.

IX. 4. 22. Preparation of 2-methoxymethoxy-4-methyl-3-(2,4,6-trimethylphenyl)deuterobenzene



The substrate (135 mg, 0.5 mmol, 1 eq.) was dissolved in dry, freshly distilled THF (0.5 ml) in a dry, two-necked flask (10 ml), under argon. It was cooled down to -78°C and *n*-BuLi (345 µl, 1.6 M in hexane, 0.55 mmol, 1.1 eq.) was added dropwise. The reaction mixture was stirred during 1 hour at -78°C and an additional 1 hour at room temperature. After 10 minutes stirring at room temperature, slightly yellow precipitate formed in the mixture. Deuterated water was added in excess at 0°C. By the addition the precipitate disappeared. Water was added and the mixture was extracted by diethyl ether. The separated organic phase was dried over $MgSO_4$, filtered and evaporated. The NMR analysis of the obtained crude product (120 mg) shows total conversion to the required deuterated compound.



Molecular formula: $C_{18}H_{21}DO_2$

Molecular weight: 271.37 g/mol

Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.89	s	-	3	17
1.92	s	-	6	18, 20
2.33	s	-	3	19
3.30	s	-	3	10
5.04	s	-	2	8
6.94	s	-	2	13, 15
6.95	d	-*	1	4
7.20	d	7.8	1	5

*Due to an extensive overlap with the singlet at δ=6.94, this coupling constant could not be accurately measured.

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
19.54	17
19.89	18, 20
21.18	19
55.65	10
94.19	8
111.70 (t, J= 90 Hz)	6
123.48	4
127.62	5
127.94	13, 15
129.93, 134.11, 136.22, 137.70	2, 3, 11, 14
135.97	12, 16
154.18	1

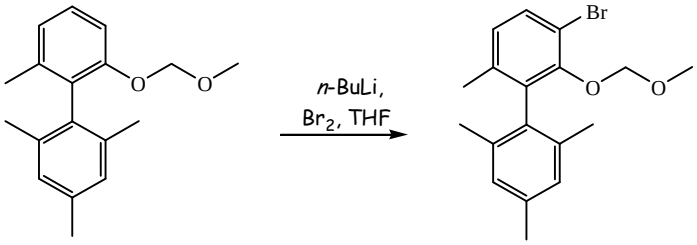
Infrared spectrum (film, cm^{-1}): 2948w, 2918w, 2856w (C-H); 1571w (aromatic C-C); 1448w; 1434w; 1390w; 1242m; 1153m; 1049s (C-O); 991m; 923w; 850w.

Mass spectrum (CI) m/z (relative intensity): 272 $[M+H]^+$ (20%), 240 (M-31, $[C_{17}H_{18}DO]^+$) (76%), 84 (M-187, $[C_6H_{12}]^+$(100%).

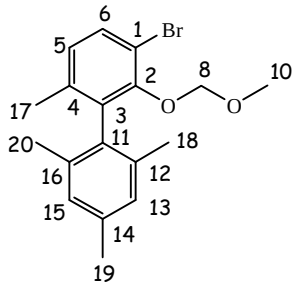
Melting point: 57-58°C

High resolution mass spectrum (ES+, M+Na): for $C_{18}H_{23}O_2Na$, calculated: 294.1596, found: 294.1593.

IX. 4. 23. Preparation of 2-methoxymethoxy-4-methyl-3-(2,4,6-trimethylphenyl)bromobenzene



The substrate (600 mg, 2.22 mmol, 1 eq.) was dissolved in dry, distilled THF (4.4 ml) in a two-necked flask (25 ml), under argon. It was cooled down to -78°C and *n*-BuLi (1 ml, 2.5 M in hexane, 2.5 mmol, 1.1 eq.) was added dropwise. After 1 hour stirring at -78°C, the reaction mixture was stirred for an additional hour at 0°C. Then it was cooled back to -78°C and bromine (4.9 ml, 0.9 M in hexane, 4.41 mmol, 2 eq.) was added dropwise. After the addition, the temperature was let warm up slowly to room temperature. Water was added and the mixture was extracted with DCM. The separated organic layer was washed with saturated aqueous solution of $Na_2S_2O_3$ and brine, dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 40 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.25) to obtain the title compound as a pure product (662 mg, *85%* yield).



Molecular formula: $C_{18}H_{21}BrO_2$

Molecular weight: 349.26 g/mol

Physical aspect: colourless oil

^{1}H-NMR (500 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.89	s	-	3	17
1.95	s	-	6	18, 20
2.31	s	-	3	19
2.93	s	-	3	10
4.73	s	-	2	8
6.92	s	-	2	13, 15
6.95	d	8.0	1	5
7.45	d	8.0	1	6

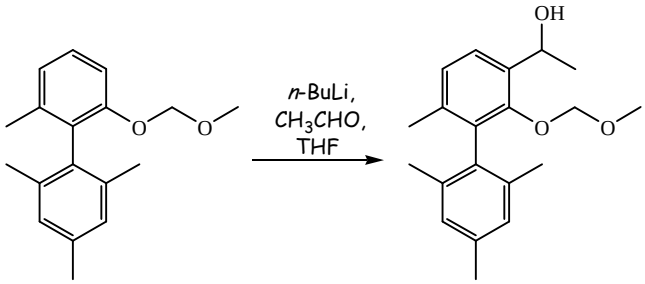
^{13}C-NMR (125 MHz, $CDCl_3$)	
δ (ppm)	N°
19.45	17
20.07	18, 20
21.06	19
56.63	10
98.36	8
114.89	1
127.12	5
128.02	13, 15
131.76	6
133.44, 136.25, 136.86, 137.63	3, 4, 11, 14
136.33	12, 16
151.34	2

Infrared spectrum (film, cm^{-1}): 2945w, 2920w, 2856w (C-H); 1610w, 1569w (aromatic C-C); 1446m; 1384m; 1244w; 1203w; 1157s (C-O); 1087w; 1020m; 970s; 927w; 908w; 850m; 802m.

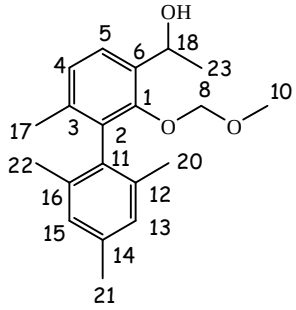
Mass spectrum (APCI) m/z (relative intensity): 349 $[M+H]^+$ (1%), 319 and 317 (M-31, $[C_{17}H_{19}BrO]^+$) (95% and 100%), 238 (M-111, $[C_{17}H_{18}O]^{\cdot +}$) (58%), 223 (M-126, $[C_{16}H_{15}]^+$) (37%).

High resolution mass spectrum (ES+, $M+Na^+$): for $C_{18}H_{21}O_2BrNa$, ^{79}Br: calculated: 371.0623, found: 371.0607, ^{81}Br: calculated: 373.0602, found: 373.0590.

IX. 4. 24. Preparation of 1-(2-(methoxymethoxy)-4-methyl-3-(2,4,6-trimethylphenyl)phenyl)ethanol



The substrate (810 mg, 3 mmol, 1 eq.) was dissolved in dry, distilled THF (6 ml) in a dry, two-necked flask under argon. The solution was cooled down to -78°C and *n*-BuLi (2.1 ml, 1.6 M in hexane, 3.3 mmol, 1.1 eq.) was added dropwise. The lemon yellow solution was stirred 1 hour at -78°C, and then the temperature was increased to 0°C during an additional 1 hour. A yellow suspension formed. Then acetaldehyde (190 µl, 3.3 mmol, 1.1 eq.) was added dropwise resulting a clear solution. After 30 minutes stirring, water was added and the mixture was extracted with diethyl ether. The organic layer was dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 2 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.22) to obtain the title compound as a pure product (740 mg, *79%* yield).



Molecular formula: $C_{20}H_{26}O_3$

Molecular weight: 314.42 g/mol

Physical aspect: colourless oil

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.56	d	6.7	3	23
1.92	s	-	3	17
1.94	s	-	3	20
1.97	s	-	3	22
2.32	s	-	3	21
3.11	bs	-	1	OH
3.26	s	-	3	10
4.45	s	-	2	8
5.20	q	6.7	1	18
6.92	s	-	2	13, 15
7.09	d	7.9	1	4
7.33	d	7.9	1	5

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
19.48	17
20.10, 20.15	20, 22
21.08	21
22.38	23
56.76	10
64.53	18
98.44	8
124.78	4
126.14	5
128.04, 128.07	13, 15
133.53, 133.62, 135.90, 135.97, 136.17, 136.53	2, 3, 11, 12, 14, 16
137.17	6
152.16	1

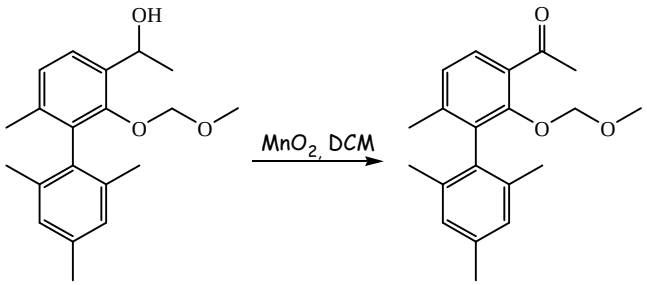
Infrared spectrum (film, cm^{-1}): 3400bs (OH); 2972w, 2921m (C-H); 1610w (aromatic C-C); 1446s; 1265w; 1157s, 1033s (C-O); 979m; 921m; 850w; 825w; 738w.

Mass spectrum (APCI) m/z (relative intensity): 297 (M-17, $[C_{20}H_{25}O_2]^+$) (10%), 265 (M-49, $[C_{19}H_{21}O]^{+)}$ (68%), 253 (M-61, $[C_{18}H_{21}O]^{+)}$ (100%), 237 (M-77, $[C_{18}H_{21}]^{+)}$ (37%).

High resolution mass spectrum (ES+, $M+Na^+$): for $C_{20}H_{26}O_3Na$, calculated: 337.1780, found: 337.1764.

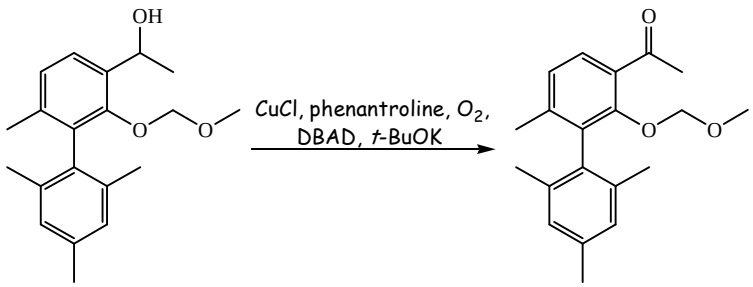
IX. 4. 25. Preparation of 1-(2-(methoxymethoxy)-4-methyl-3-(2,4,6-trimethylphenyl)phenyl)ethanone

Procedure A:

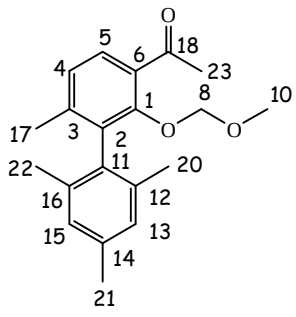


The alcohol (455 mg, 1.45 mmol, 1 eq.) was dissolved in DCM (10 ml) in a one-necked flask (50 ml). MnO_2 (500 mg, 5.75 mmol, 4 eq.) was added to the solution and it was stirred at room temperature overnight until complete conversion. The reaction mixture was filtered through a short pad of celite and the collected organic layer was evaporated to obtain the title compound as a pure product (430 mg, *95%* yield).

Procedure B:



1,10-Phenantroline (27 mg, 0.15 mmol, 0.05 eq.) and CuCl (15 mg, 0.15 mmol, 0.005 eq.) were added to fluorobenzene (30 ml) in a three-necked flask (100 ml) equipped with a refrigerator and a gas inlet, and connected to a bubbler. After 5 minutes stirring at room temperature, the substrate (943 mg, 3.0 mmol, 1 eq.) and *t*-BuOK (17 mg, 0.15 mmol, 0.05 eq.) were added. After 10 minutes additional stirring, DBAD (35 mg, 0.15 mmol, 0.05 eq.) was added and the mixture was heated up to 75-80°C under a gentle O_2 stream. Since the reaction was not complete after 5 hours, it was left for overnight. For that, the stream was stopped and the O_2 atmosphere was maintained by a balloon. After the overnight reaction, a 4 to 1 mixture of celite-silice (600 mg) was added and stirring was continued for a few minutes. Then the celite-silice mixture was filtered-off and washed with diethyl ether. The collected organic layer was evaporated to obtain the crude product (969 mg). The resulted crude was purified by flash column chromatography using a 4 to 1 mixture of petrol ether and ethyl acetate as eluent to obtain the title compound as a pure product (552 mg, *59%* yield).



Molecular formula: $C_{20}H_{24}O_3$

Molecular weight: 312.40 g/mol

Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.97	s	-	9	17, 20, 22
2.32	s	-	3	21
2.63	s	-	3	23
2.94	s	-	3	10
4.60	s	-	2	8
6.90	s	-	2	13, 15
7.13	d	7.7	1	4
7.52	d	7.7	1	5

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
19.98	17
20.13	20, 22
21.07	21
30.56	23
56.68	10
99.41	8
125.83	4
128.00	13, 15
128.24	5
131.98, 133.00, 134.86, 136.72, 142.60	2, 3, 6, 11, 14
136.12	12, 16
153.03	1
200.71	18

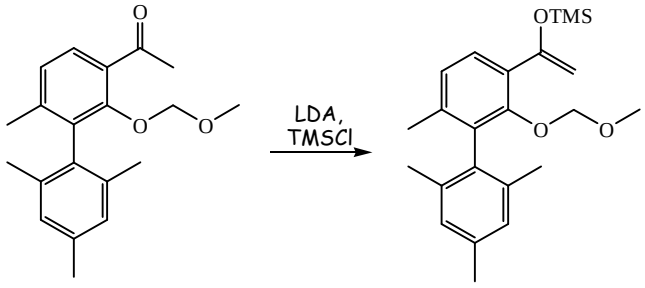
Infrared spectrum (film, cm^{-1}): 2997w, 2948w, 2920w (C-H); 1683s (C=O); 1633s; 1595w (aromatic C-C); 1436s; 1363m; 1319s; 1286w; 1244s (C-O); 1159m; 1035w; 1024w; 981m; 850w; 802w.

Mass spectrum (APCI) m/z (relative intensity): 281 (M-31, $[C_{19}H_{21}O_2]^+$) (25%), 269 (M-43, $[C_{18}H_{21}O_2]^{+)}$ (100%), 251 (M-61, $[C_{18}H_{20}O]^{+)}$ (35%), 239 (M-73, $[C_{17}H_{19}O]^{+)}$ (21%).

Melting point: 67-69°C

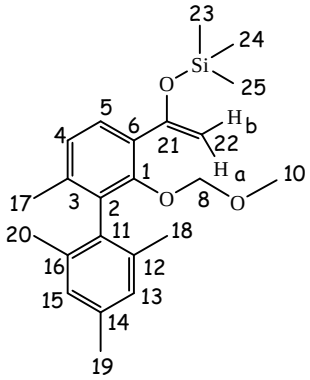
Elementary analysis: calculated: C: 76.90%, H: 7.74%; found: C: 76.74%, H: 7.85%.

IX. 4. 26. Preparation of (1-(2-(methoxymethoxy)-4-methyl-3-(2,4,6-trimethylphenyl)phenyl)vinyloxy)trimethylsilane



Dry, freshly distilled THF (1 ml) was placed in a two-necked, flame-dried flask (25 ml) under argon. It was cooled down to °0 C and diisopropylamine (90 µl, 0.62 mmol, 1.25 eq.) was added followed by *n*-BuLi (375 µl, 1.6 M in hexane, 0.60 mmol, 1.20 eq.). After 30 minutes stirring at 0°C, the mixture was cooled down to -78°C and the ketone (156 mg, 0.5 mmol, 1 eq.) dissolved in dry THF (0.4 ml) was added dropwise. The temperature was kept between -78°C and -60°C during 1 hour, and then TMSCl (100 µl, 0.8 mmol, 1.6 eq.) was added dropwise. The mixture was let warm up slowly to 0°C, and kept at that temperature during 30 minutes. Aqueous, saturated solution of $NaHCO_3$ was added to the mixture, and it was extracted by diethyl ether. The separated organic phase was dried over Na_2SO_4, filtered and evaporated. The NMR analysis of the obtained crude product showed nearly complete conversion to the silylenol ether.

Using KHMDS as base gave similar results. Contrary to that, using NaH as base, the starting material was recovered.



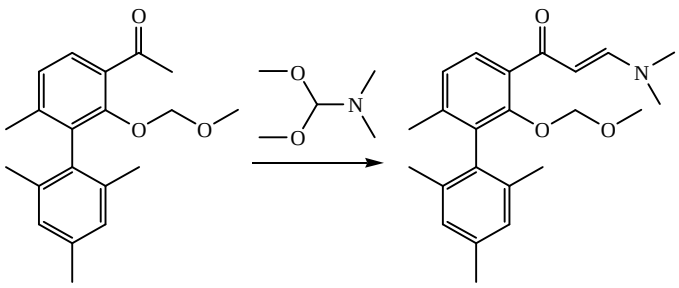
Molecular formula: $C_{23}H_{32}O_3Si$

Molecular weight: 384.58 g/mol

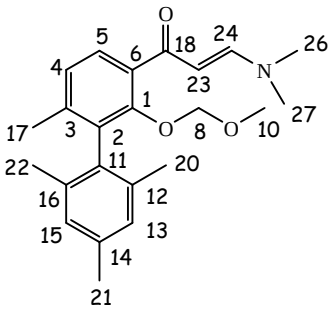
Physical aspect: colourless oil

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
0.12	s	-	9	23, 24, 25
1.89	s	-	3	17
1.94	s	-	6	18, 20
2.74	s	-	3	19
2.77	s	-	3	10
4.55	s	-	1	22a or 22b
4.69	s	-	2	8
4.90	s	-	1	22a or 22b
6.88	s	-	2	13, 15
7.00	d	7.8	1	4
7.33	d	8.1	1	5

IX. 4. 27. Preparation of 3-(dimethylamino)-1-(2-(methoxymethoxy)-4-methyl-3-(2,4,6-trimethylphenyl)phenyl)prop-2-en-1-one



Mixture of the ketone (156 mg, 0.5 mmol, 1 eq.) and *N*,*N*-dimethylformamide-dimethylacetal (140 µl, 1 mmol, 2 eq.) was refluxed at 110°C during 24 hours in a one-necked flask (5 ml) equipped with a condenser. Then, it was concentrated on the vacuum pump and the residue was dissolved in DCM. It was washed with brine, dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using ethyl acetate as eluent (R_f = 0.21) to obtain the title compound as a pure product (141 mg, *77%* yield).



Molecular formula: $C_{23}H_{29}NO_3$

Molecular weight: 367.48 g/mol

Physical aspect: yellow oil

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.95	s	-	3	17
1.98	s	-	6	20, 22
2.30	s	-	3	21
2.82	s	-	3	10
2.86	bs	-	3	26, 27
3.06	bs	-	3	
4.69	s	-	2	8
5.54	d	12.2	1	23
6.92	s	-	2	13, 15
7.09	d	7.7	1	4
7.26 - 7.30	bm	-	2	5, 24

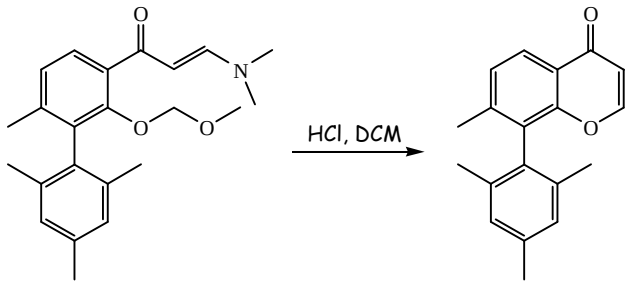
^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
19.83	17
20.20	20, 22
21.08	21
37.11, 44.92	26, 27
56.26	10
97.52	23
99.31	8
125.58	4
127.77	13, 15
128.04	5
133.60, 133.72, 134.27, 136.27, 139.34	2, 3, 6, 11, 14
136.16	12, 16
151.47	1
154.63	24
191.70	18

Infrared spectrum (film, cm^{-1}): 2920m, 2856w (C-H); 1643s (C=O); 1573m (aromatic C-C); 1434m; 1269s; 1155m; 1097s (C-O); 1037w; 977s; 923m.

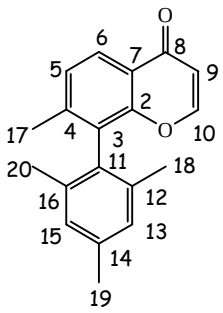
Mass spectrum (APCI) m/z (relative intensity): 368 $[M+H]^+$ (53%), 336 (M-31, $[C_{22}H_{26}NO_2]^+$) (28%), 297 (M-70, $[C_{19}H_{21}O_3]^{+)}$ (33%), 253 (M-114, $[C_{17}H_{17}O_2]^{+)}$ (100%).

High resolution mass spectrum (ES+, $M+H^+$): for $C_{23}H_{30}NO_3$, calculated: 368.2226, found: 368.2218.

IX. 4. 28. Preparation of 8-(2,4,6-trimethylphenyl)-7-methyl-4H-chromen-4-one



The enaminone (930 mg, 2.5 mmol, 1 eq.) was dissolved in DCM (20 ml) in a one-necked flask equipped with a condenser. Concentrated HCl solution (2 ml) was added and the mixture was refluxed for 2 hours. Then, it was let cool down to room temperature and water was added. The two layers were separated and the organic layer was washed with aqueous, saturated solution of $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 4 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.30) to obtain the title compound as a pure product (600 mg, *85%* yield).



Molecular formula: $C_{19}H_{18}O_2$

Molecular weight: 278.35 g/mol

Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.85	s	-	6	18, 20
2.05	s	-	3	17
2.33	s	-	3	19
6.25	d	6.5	1	9
6.98	s	-	2	13, 15
7.34	d	7.9	1	5
7.65	d	6.5	1	10
8.11	d	7.9	1	6

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
19.84	17, 18, 20
21.17	19
112.35	9
122.94	7
124.14	5
127.18	6
128.21	13, 15
129.38, 131.02, 137.41, 143.32,	3, 4, 11, 14
135.89	12, 16
153.71	2
155.16	10
177.62	8

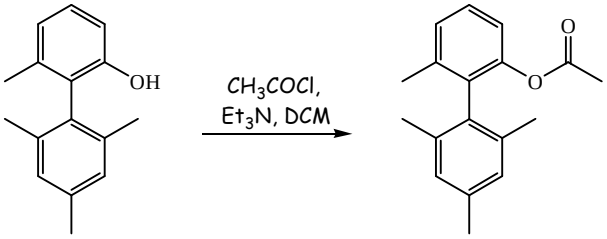
Infrared spectrum (film, cm^{-1}): 3064w, 2968w, 2918w, 2858w (C-H); 1650s (C=O); 1612w, 1591m (aromatic C-C); 1566m; 1411m; 1332s; 1245m; 1186m; 1045w; 1004w; 865w; 850w; 821m.

Mass spectrum (APCI) m/z (relative intensity): 279 $[M+H]^+$ (100%).

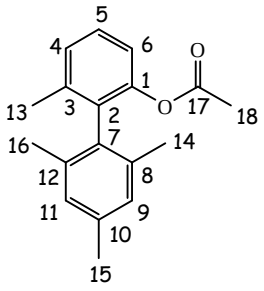
Melting point: 134-136°C

Elementary analysis: calculated: C: 81.99%, H: 6.52%; found: C: 81.64%, H: 6.33%.

IX. 4. 29. Preparation of 1-(3-methyl-2-(2,4,6-trimethylphenyl)phenyl)acetate



The hydroxy biphenyl (226 mg, 1 mmol, 1 eq.) was dissolved in DCM (5 ml) in a one-necked flask (25 ml). It was cooled down to 0°C and triethylamine (150 µl, 1.1 mmol, 1.1 eq.) was added followed by acetyl chloride (80 µl, 1.1 mmol, 1.1 eq.). The mixture was let warm up to room temperature and stirred during 2 hours. Then, water was added and extraction was carried out with DCM. The organic layer was dried over Na_2SO_4, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 10 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.69) to obtain the title compound as a pure product (250 mg, *93%* yield).



Molecular formula: $C_{18}H_{20}O_2$

Molecular weight: 268.35 g/mol

Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.83	s	-	3	13
1.91	s	-	6	14, 16
1.98	s	-	3	18
2.31	s	-	3	15
6.89	s	-	2	9, 11
6.98	d	7.9	1	4
7.17	d	7.3	1	6
7.27	t	7.6	1	5

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
19.44	13
19.70	14, 16
20.41	18
21.07	15
119.91	6
127.45	4
127.69	5
127.97	9, 11
136.23	8, 12
132.32, 133.42, 136.63, 138.22	2, 3, 7, 10
148.55	1
169.29	17

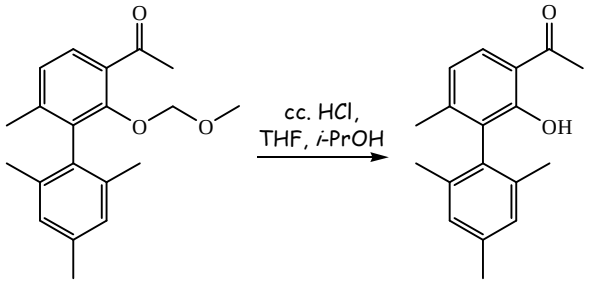
Infrared spectrum (film, cm^{-1}): 3010w, 2947w, 2920w (C-H); 1766s (C=O); 1608w, 1575w (aromatic C-C); 1460m; 1365m; 1197s (CO-O); 1026m; 954w; 850w; 794w; 761w.

Mass spectrum (APCI) m/z (relative intensity): 269 $[M+H]^+$ (33%), 227 (M-41, $[C_{16}H_{19}O]^+$) (100%), 194 (M-74, $[C_{15}H_{14}O]^{\cdot +}$) (8%).

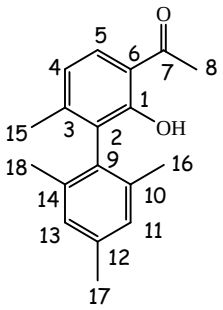
Melting point: 45-46°C

Elementary analysis: calculated: C: 80.57%, H: 7.51%; found: C: 80.42%, H: 7.49%.

IX. 4. 30. Preparation of 1-(2-hydroxy-4-methyl-3-(2,4,6-trimethyl-phenyl)phenyl)ethanone



The ketone (2.00 g, 6.4 mmol, 1 eq.) was dissolved in the mixture of THF (6.4 ml) and *i*-PrOH (6.4 ml) in a one-necked flask (25 ml). It was cooled down to 0°C and concentrated aqueous solution of HCl (1.2 ml, 32 mmol, 5 eq.) was added. The mixture was let warm up to room temperature and stirred overnight. Then, water was added to the red solution and it was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 4 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.70) to obtain the title compound as a pure product (1.69 g, *99%* yield).



Molecular formula: $C_{18}H_{20}O_2$

Molecular weight: 268.35 g/mol

Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.93	s	-	6	16, 18
1.99	s	-	3	15
2.32	s	-	3	17
2.64	s	-	3	8
6.85	d	8.2	1	4
6.96	s	-	2	11, 13
7.66	d	8.2	1	5
12.47	s	-	1	OH

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
19.72	16, 18
20.16	15
21.12	17
26.54	8
117.63	6
120.54	4
128.26	11, 13
129.30	5
135.93	10, 14
129.47, 132.16, 136.93, 146.27	2, 3, 9, 12
159.73	1
204.02	7

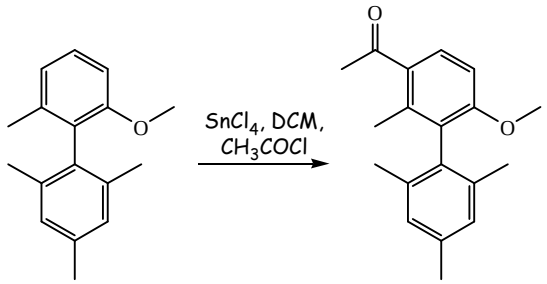
Infrared spectrum (film, cm^{-1}): 2999w, 2947w, 2918w (C-H); 1631s (C=O); 1573w, 1494w (aromatic C-C); 1434m; 1363s; 1317s; 1242s (C-O); 1195w; 1166w; 1139w; 1022w; 981w; 848w; 800m.

Mass spectrum (APCI) m/z (relative intensity): 269 $[M+H]^+$ (100%), 251 (M-17, $[C_{18}H_{19}O]^+$) (78%), 236 (M-32, $[C_{17}H_{16}O]^{\cdot +}$) (17%).

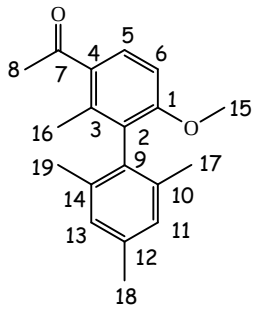
Melting point: 104-107°C

Elementary analysis: calculated: C: 80.57%, H: 7.51%; found: C: 80.52%, H: 7.58%.

IX. 4. 31. Preparation of 1-(4-methoxy-2-methyl-3-(2,4,6-trimethyl-phenyl)phenyl)ethanone



The methoxy biphenyl (120 mg, 0.5 mmol, 1 eq.) was dissolved in dry, distilled DCM (1 ml) in a dry, one-necked flask (10 ml). It was cooled down to 0°C and treated with a mixture of $SnCl_4$ (1.5 ml, 1 M in DCM, 1.5 mmol, 3 eq.) and acetyl chloride (45 µl, 0.6 mmol, 1.2 eq.) in dry, distilled DCM (1.5 ml). After 1 hour stirring at 0°C, the reaction was quenched by the addition of aqueous $NaHCO_3$ solution. Extraction was carried out using DCM. The organic layer was dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 20 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.10) to obtain the title compound as a pure product (98 mg, *69%* yield).



Molecular formula: $C_{19}H_{22}O_2$

Molecular weight: 282.38 g/mol

Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.86	s	-	6	17, 19
2.10	s	-	3	16
2.33	s	-	3	18
2.60	s	-	3	8
3.75	s	-	3	15
6.85	d	8.7	1	6
6.94	s	-	2	11, 13
7.79	d	8.7	1	5

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
17.41	16
19.83	17, 19
21.15	18
29.60	8
55.69	15
107.06	6
128.05	11, 13
130.89	5
136.01	10, 14
130.63, 131.29, 133.41, 136.54, 139.13	2, 3, 4, 9, 12
159.18	1
200.73	7

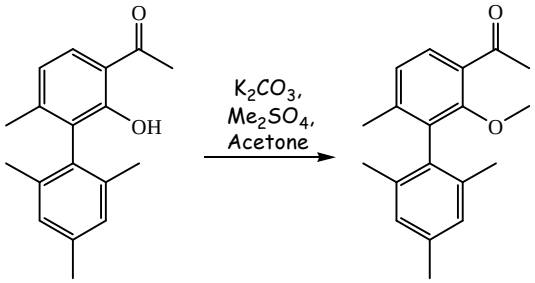
Infrared spectrum (film, cm^{-1}): 3001w, 2939w, 2839w (C-H); 1676s (C=O); 1571s (conjugated C-C); 1442m; 1352w; 1261s (C-O); 1232m; 1182w; 1147w; 1083s (C-O); 1000w; 850w; 808m.

Mass spectrum (APCI) m/z (relative intensity): 283 $[M+H]^+$ (100%), 241 (M-41, $[C_{17}H_{21}O]^+$) (99%); 226 (M-56, $[C_{16}H_{18}O]^{\cdot +}$) (23%).

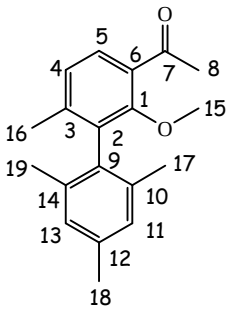
Melting point: 46-49°C

Elementary analysis: calculated: C: 80.82%, H: 7.85%; found: C: 80.77%, H: 7.97%.

IX. 4. 32. Preparation of 1-(2-methoxy-4-methyl-3-(2,4,6-trimethyl-phenyl)phenyl)ethanone



The hydroxy ketone (1.61 g, 6 mmol, 1 eq.) was dissolved in acetone (10 ml) in a two-necked flask (25 ml) equipped with a condenser. K_2CO_3 (1.66 g, 12 mmol, 2 eq.) was added followed by Me_2SO_4 (1.2 ml, 12 mmol, 2 eq.). The mixture was refluxed overnight. Then K_2CO_3 was filtered off and water was added to the residue. It was extracted with diethyl ether. The organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated. The resulted crude product was purified by normal column chromatography using a 100 to 1 mixture of petrol ether and methanol as eluent (R_f = 0.57) to obtain the title compound as a pure product (1.37 g, *81%* yield).



Molecular formula: $C_{19}H_{22}O_2$

Molecular weight: 282.38 g/mol

Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.95	s	-	3	16
1.97	s	-	6	17, 19
2.34	s	-	3	18
2.62	s	-	3	8
3.38	s	-	3	15
6.96	s	-	2	11, 13
7.10	d	7.9	1	4
7.59	d	7.9	1	5

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
19.74	16
20.12	17, 19
21.09	18
30.70	8
60.83	15
125.67	4
128.28	11, 13
128.63	5
135.93	10, 14
130.94, 133.06, 134.59, 136.92, 143.14	2, 3, 6, 9, 12
156.99	1
200.54	7

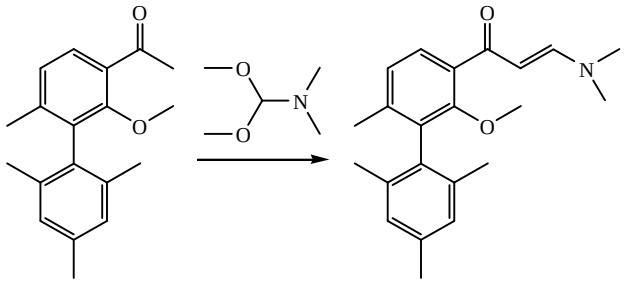
Infrared spectrum (film, cm^{-1}): 2999w, 2920w (C-H); 1677s (C=O); 1593m (conjugated C-C); 1454m; 1388m; 1355m; 1286s, 1236s (C-O); 1194m; 1126m; 1056m; 1041w; 850m; 821w.

Mass spectrum (APCI) m/z (relative intensity): 283 $[M+H]^+$ (100%), 265 (M-17, $[C_{19}H_{21}O]^+$) (42%); 250 (M-32, $[C_{18}H_{18}O]^{\cdot +}$) (33%); 241 (M-41, $[C_{17}H_{21}O]^+$) (13%); 237 (M-45, $[C_{17}H_{17}O]^+$) (20%).

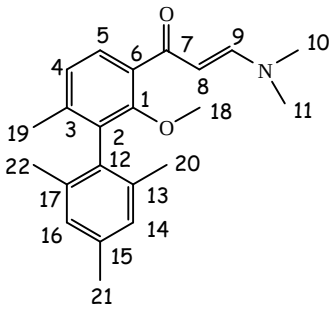
Melting point: 50-54°C

Elementary analysis: calculated: C: 80.82%, H: 7.85%; found: C: 80.96%, H: 7.96%.

IX. 4. 33. Preparation of 3-(dimethylamino)-1-(2-methoxy-4-methyl-3-(2,4,6-trimethylphenyl)phenyl)prop-2-en-1-one



Mixture of the ketone (1.20 g, 4.25 mmol, 1 eq.) and *N*,*N*-dimethylformamide-dimethylacetal (1.80 ml, 12.75 mmol, 3 eq.) was refluxed at 110°C during 24 hours in a one-necked flask (5 ml) equipped with a condenser. Then, it was concentrated on the vacuum pump and the residue was dissolved in DCM. It was washed with brine, dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using ethyl acetate as eluent (R_f = 0.29) to obtain the title compound as a pure product (1.24 g, *86%* yield).



Molecular formula: $C_{22}H_{27}NO_2$

Molecular weight: 337.46 g/mol

Physical aspect: yellow solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.93	s	-	3	19
1.97	s	-	6	20, 22
2.33	s	-	3	21
2.85, 3.05	2 bs	-	6	10, 11
3.45	s	-	3	18
5.62	d	11.5	1	8
6.95	s	-	2	14, 16
7.07	d	7.8	1	4
7.32 - 7.70	bm	-	2	5, 9

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
19.51	19
20.11	20, 22
21.05	21
37.03, 44.81	10, 11
61.33	18
97.61	8
125.30	4
128.05	14, 16
135.70	5
136.35	13, 17
128.35, 133.01, 133.74, 133.90, 139.50	2, 3, 6, 12, 15
154.67	9
154.94	1
191.33	7

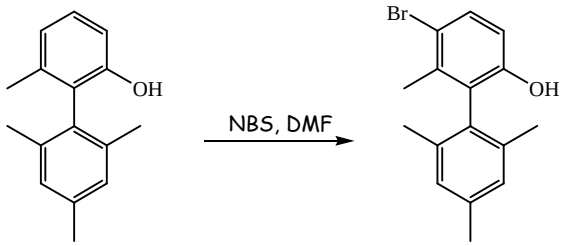
Infrared spectrum (film, cm^{-1}): 2918m (C-H); 1643s (C=O); 1593w, 1569m (aromatic C-C); 1550w; 1433m; 1348s; 1269s; 1234w; 1091s (C-O); 1058w; 1043w; 925w; 898w; 850w; 798w; 730m.

Mass spectrum (APCI) m/z (relative intensity): 338 $[M+H]^+$ (100%), 267 (M-70, $[C_{18}H_{19}O_2]^+$) (63%).

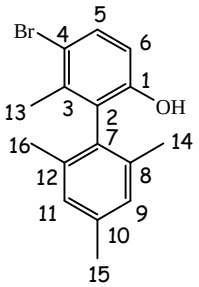
Melting point: 98-101°C

High resolution mass spectrum (ES+, $M+H^+$): for $C_{22}H_{28}NO_2$, calculated: 338.2120, found: 338.2107.

IX. 4. 34. Preparation of 4-bromo-3-methyl-2-(2,4,6-trimethylphenyl)phenol



The hydroxy biphenyl (226 mg, 1 mmol, 1 eq.) was dissolved in dry DMF (5 ml) in a two-necked flask (25 ml) under argon. *N*-bromo-succinimide (178 mg, 1 mmol, 1 eq.) dissolved in dry DMF (5 ml) was added dropwise. After overnight stirring at room temperature, water was added and the mixture was extracted with DCM. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 25 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.16) to obtain the title compound as a pure product (190 mg, *62%* yield).



Molecular formula: $C_{16}H_{17}BrO$

Molecular weight: 305.21 g/mol

Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.93	s	-	6	14, 16
1.99	s	-	3	13
2.34	s	-	3	15
4.49	s	-	1	OH
6.75	d	8.7	1	6
7.00	s	-	2	9, 11
7.44	d	8.7	1	5

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
19.73	14, 16
19.90	13
21.11	15
114.04	6
115.77	4
129.10	9, 11
132.10	5
137.58	8, 12
127.75, 130.09, 136.37, 138.54	2, 3, 7, 10
151.66	1

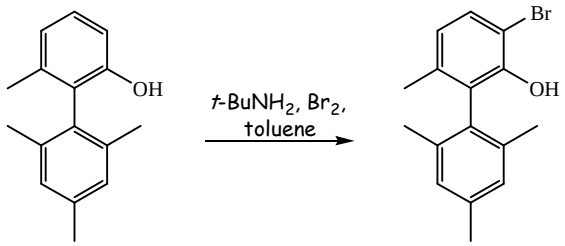
Infrared spectrum (film, cm^{-1}): 3519m, 3487m (OH); 2997w, 2945w, 2918w (C-H); 1612w, 1568m (aromatic C-C); 1456s; 1377w; 1319w; 1274s; 1249m; 1176s(C-O); 1022m; 852m; 811m.

Mass spectrum (APCI) m/z (relative intensity): 305 and 307 $[M+H]^+$ (20%), 226 (M-78, $[C_{16}H_{18}O]^{\cdot +}$) (100%), 211 (M-93, $[C_{16}H_{19}]^+$) (68%), 194 (M-110, $[C_{15}H_{14}]^{\cdot +}$) (11%).

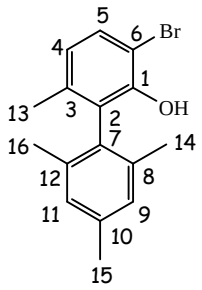
Melting point: 95-97°C

Elementary analysis: calculated: C: 62.97%, H: 5.61%; found: C: 63.39%, H: 5.69%.

IX. 4. 35. Preparation of 6-bromo-3-methyl-2-(2,4,6-trimethylphenyl)phenol



Dry, freshly distilled toluene (12 ml) and dry, freshly distilled *t*-$BuNH_2$ (2.5 ml, 24 mmol, 2 eq.) were placed in a two-necked, flame-dried flask (50 ml) under argon and cooled down to -30°C. Bromine (620 µl, 12 mmol, 1 eq.) was added dropwise. The reaction was kept between -30 and -10°C during 30 min. Then, it was cooled down to -78°C and the substrate (2.72 g, 12 mmol, 1 eq.) dissolved in DCM (2 ml) was added dropwise. At the moment of the addition a yellow suspension was formed, which changed into an orange clear solution in a few minutes. The reaction was kept during 2 hours at -78°C and very slowly (~5h) let warm to room temperature. The reaction was quenched by the addition of water, and then extracted with DCM. The organic layer was washed with saturated $Na_2S_2O_3$ solution and brine, dried over Mg_2SO_4, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 25 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.26) to obtain the title compound as a pure product (1.99 g, *54%* yield).



Molecular formula: $C_{16}H_{17}BrO$

Molecular weight: 305.21 g/mol

Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.88	s	-	3	13
1.94	s	-	6	14, 16
2.34	s	-	3	15
5.08	s	-	1	OH
6.77	d	8.2	1	4
6.99	s	-	2	9, 11
7.37	d	8.2	1	5

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
19.25	13
19.69	14, 16
21.14	15
106.45	6
123.06	4
128.78	9, 11
130.98	5
136.82	8, 12
127.72, 131.02, 137.09, 137.95	2, 3, 7, 10
149.07	1

Infrared spectrum (film, cm^{-1}): 3510s (OH); 2968m, 2918m (C-H); 1610w; 1568w; 1440m; 1377w; 1313m; 1265m; 1234m; 1170m; 1126s (C-O); 1035m; 1014m; 950w; 850m; 794m; 777w; 746w.

Mass spectrum (APCI) m/z (relative intensity): 305 and 307 $[M+H]^+$ (2%), 288 and 290 (M-16, $[C_{16}H_{17}Br]^{\cdot+}$) (12%), 226 (M-78, $[C_{16}H_{18}O]^{\cdot+}$) (100%), 210 (M-94, $[C_{16}H_{18}]^{\cdot+}$) (5%).

Melting point: 81-82°C

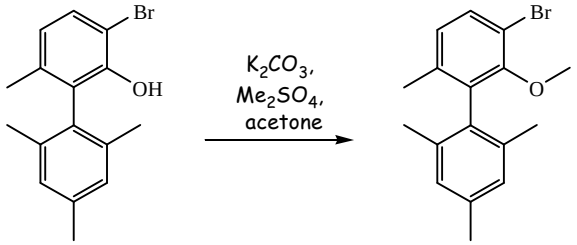
Elementary analysis: calculated: C: 62.97%, H: 5.61%; found: C: 62.93%, H: 5.64%.

IX. 4. 36. Preparation of 1-bromo-2-methoxy-4-methyl-3-(2,4,6-trimethylphenyl)benzene

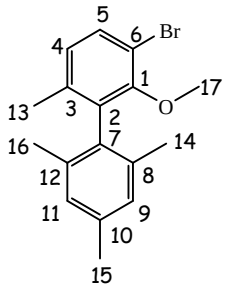
Procedure A:

The methoxy biphenyl (120 mg, 0.5 mmol, 1 eq.) was dissolved in dry, freshly distilled diethyl ether (5 ml) in a two-necked flask (25 ml) under argon. Distilled TMEDA (150 µl, 1 mmol, 2 eq.) was added followed by *n*-BuLi (400 µl, 2.5 M in hexane, 1 mmol, 2 eq.). The reaction was stirred at room temperature during 2 hours. Then, it was cooled down to -78°C and bromine (1.2 ml, 0.9 M in hexane, 1 mmol, 2 eq.) was added dropwise. The mixture was allowed to warm up slowly to room temperature. The reaction was quenched by water and extracted with DCM. The organic layer was washed with saturated aqueous solution of $Na_2S_2O_3$ and brine, dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 40 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.63) to obtain the title compound as a pure product (47 mg, *29%* yield).

Procedure B:



The substrate (806 mg, 2.64 mmol, 1 eq.) was dissolved in acetone (10 ml) in a condenser-equipped, two-necked flask (25 ml). K_2CO_3 (2.52 g, 18.23 mmol, 7 eq.) and Me_2SO_4 (740 µl, 7.82 mmol, 3 eq.) were added subsequently, and the mixture was refluxed overnight. Then K_2CO_3 was filtered off, water was added and extraction was carried out using DCM. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 40 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.63) to obtain the title compound as a pure product (790 mg, *94%* yield).



Molecular formula: $C_{17}H_{19}BrO$

Molecular weight: 319.24 g/mol

Physical aspect: colourless oil

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.87	s	-	3	13
1.95	s	-	6	14, 16
2.33	s	-	3	15
3.44	s	-	3	17
6.93	d	8.2	1	4
6.94	s	-	2	9, 11
7.45	d	8.2	1	5

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
19.17	13
20.09	14, 16
21.11	15
59.92	17
114.53	6
126.79	4
128.16	9, 11
131.66	5
135.78	8, 12
133.28, 135.97, 136.84, 137.56	2, 3, 7, 10
154.05	1

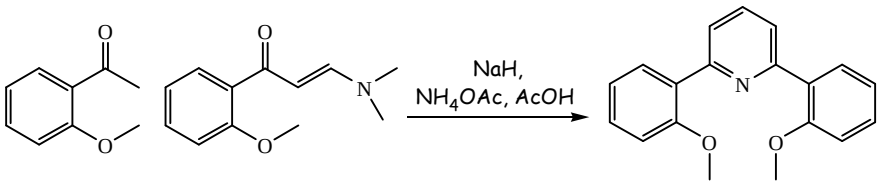
Infrared spectrum (film, cm^{-1}): 2997w, 2920m, 2856w (C-H); 1612w; 1571w; 1456s; 1390m; 1249s (C-O); 1209m; 1054s (C-O); 1020w; 918m; 850m; 802m; 784w; 771w.

Mass spectrum (APCI) m/z (relative intensity): 321 and 319 $[M+H]^+$ (62%), 306 and 304 (M-14, $[C_{16}H_{17}BrO]^{\cdot+}$) (68%), 240 (M-78, $[C_{17}H_{20}O]^{\cdot+}$) (100%), 225 (M-93, $[C_{16}H_{17}O]^+$) (65%), 210 (M-108, $[C_{16}H_{18}]^{\cdot+}$) (37%).

High resolution mass spectrum (ES+, $M+H^+$): for $C_{17}H_{20}OBr$, ^{79}Br: calculated: 319.0698, found: 319.0692, ^{81}Br: found: 321.0689.

IX. 4. 37. Preparation of 2,6-bis(2-methoxyphenyl)pyridine

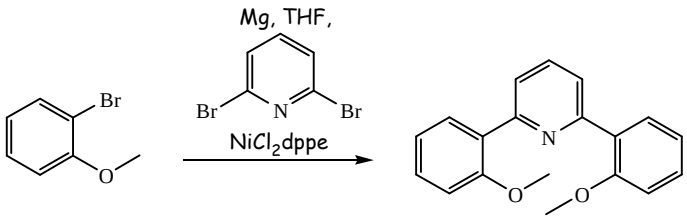
Procedure A:



NaH (98 mg, 60 w/w%, 2.44 mmol, 2 eq.) was suspended in dry, distilled THF (10 ml) in a two-necked flask (50 ml) under argon. 2-Methoxy-acetophenone (170 µl, 1.22 mmol, 1 eq.) was added to the suspension dropwise. During the addition bubbling was observed. After 15 minutes stirring at room temperature, the enaminone (500 mg, 2.44 mmol, 2 eq.) was added dropwise. The orange mixture was stirred at room temperature overnight. After a few hours, some precipitation appeared in the solution. Then, glacial acetic acid (6.1 ml, 5 ml/mmol 2-methoxy-acetophenone) was added followed by ammonium acetate (940 mg, 12.2 mmol, 10 eq.). The mixture was refluxed at 110°C during 2 hours. Then it was let cool down to room

temperature, concentrated on the vacuum pump and re-dissolved in DCM. It was washed with saturated aqueous solution of $NaHCO_3$, dried over Na_2SO_4, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 9 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.22) to obtain the title compound as a pure product (290 mg, *82%* yield).

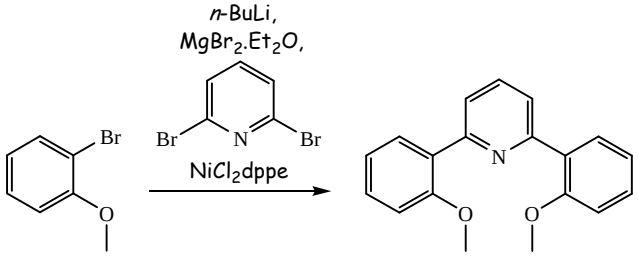
Procedure B:



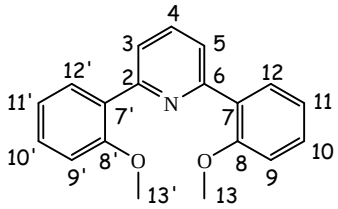
Magnesium powder (243 mg, 10 mmol, 1 eq.) was placed in a two-necked, flame-dried flask (25 ml) under argon. Dry, distilled THF (15 ml) was added, followed by the dropwise addition of *ortho*-bromo-anisole (1.87 g, 10 mmol, 1 eq.). The mixture was stirred 3 hours at room temperature to obtain a grey solution. Meantime, 2,6-dibromopyridine (1.2 g, 5 mmol, 0.5 eq.) and $NiCl_2$dppe (173 mg, 0.33 mmol, 3.3 mol%) were placed in a condenser equipped, dry, two-necked flask (50 ml), under argon. Dry, freshly distilled THF (13 ml) was added and it was cooled down to 0°C. The previously prepared magnesium reagent was added dropwise. After 30 minutes stirring at 0°C, it was let warm up to room temperature and stirred overnight. White precipitate appeared in the orange solution. It was quenched by the addition of saturated NH_4Cl solution, extracted with DCM, dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 5 to 1 mixture of

petrol ether and ethyl acetate as eluent (R_f = 0.39) to obtain the title compound as a pure product (1.1 g, *75%* yield).

Procedure C:



2-Bromoanisole (0.25 ml, 2 mmol, 1 eq.) was placed in a dry, two-necked flask (50 ml) under argon. Dry, freshly distilled diethyl ether (10 ml) was added and the solution was treated with *n*-BuLi (1.5 ml, 1.6 M in hexane, 2.4 mmol, 1.2 eq.). By the addition the mixture turned to yellow. After 30 min stirring at room temperature, a diethyl ether solution (5 ml) of $MgBr_2.Et_2O$ (568 mg, 2.2 mmol, 1.1 eq.) was added dropwise. The colour of the solution turned immediately to white. Meantime, 2,6-dibromopyridine (240 mg, 1 mmol, 0.5 eq.) and $NiCl_2$dppe (106 mg, 0.1 mmol, 0.1 eq.) were placed in a condenser-equipped, dry, two-necked flask (50 ml), under argon. Dry, freshly distilled THF (10 ml) was added and it was cooled down to 0°C. The previously prepared magnesium reagent was added dropwise. Then the mixture was heated at 65-70°C overnight. It was quenched by the addition of saturated NH_4Cl solution, extracted with DCM, dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using dichloromethane as eluent (R_f = 0.19) to obtain the title compound as a pure product (175 mg, *60%* yield).



Registry number: 195813-55-9

Molecular formula: $C_{19}H_{17}NO_2$

Molecular weight: 291.34 g/mol

Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
3.87	s	-	6	13, 13’
6.99	dd	8.3, 0.6	2	9, 9’
7.08	dt	7.5, 1.1	2	11, 11’
7.35	ddd	8.2, 7.4, 1.8	2	10, 10’
7.65-7.80	m	-	3	3, 4, 5
7.93	dd	7.6, 1.8	2	12, 12’

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
55.62	13, 13’
111.38	9, 9’
121.03	3, 5
123.05	11, 11’
129.56	7, 7’
129.62	10, 10’
131.47	12, 12’
135.12	4
155.36	2, 6
157.08	8, 8’

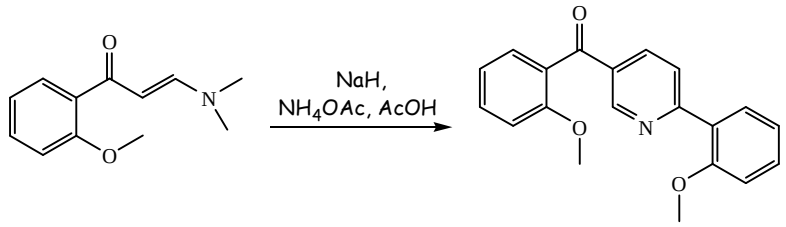
Infrared spectrum (film, cm^{-1}): 2933w, 2835w (C-H); 1598m, 1581m, 1566m (aromatic C-C); 1490s; 1461m; 1442m; 1242s; 1163w; 1122w; 1095w; 1056w; 1024s; 815w; 794w; 752s.

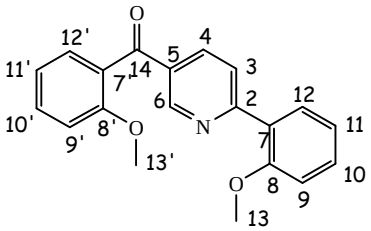
Mass spectrum (APCI) m/z (relative intensity): 292 $[M+H]^+$ (100%), 276 (M-15, $[C_{18}H_{14}NO_2]^+$) (19%), 247 (M-44, $[C_{17}H_{13}NO]^{\cdot +}$) (10%).

Melting point: 122-123°C

Elementary analysis: calculated: C: 78.33%, H: 5.88%, N: 4.81%; found: C: 77.97%, H: 5.82%, N: 4.73%.

In procedure A (***2-methoxyphenyl)(6-(2-methoxyphenyl)pyridine-3-yl)methanone*** formed as byproduct (R_f = 0.15; PE/EtOAc = 4/1) from the combination of two enaminone molecules:





Molecular formula: $C_{20}H_{17}NO_3$

Molecular weight: 319.35 g/mol

Physical aspect: yellow solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
3.74	s	-	3	13’
3.88	s	-	3	13
7.01	dd	8.2, 2.7	2	9, 9’
7.04-7.13	m	-	2	11, 11’
7.34-7.56	m	-	3	10, 10’, 12’
7.89	dd	7.7, 1.8	1	12
7.99	dd	8.3, 0.6	1	3
8.16	dd	8.3, 2.3	1	4
8.99	dd	2.1, 0.6	1	6

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
55.51	13’
55.56	13
111.41, 111.46	9, 9’
120.75, 121.07	11, 11’
124.48	3
127.99, 128.04	7, 7’
129.83	10
130.79, 131.36, 132.53	10’, 12, 12’
130.91	5
136.30	4
151.14	6
157.28, 157.37	2, 8
159.27	8’
194.78	14

Infrared spectrum (film, cm^{-1}): 3072w, 3004w, 2940w, 2837w (C-H); 1662s (C=O); 1598m, 1588m (aromatic C-C); 1490w; 1463w; 1435w; 1371m; 1301w; 1246m; 1181w; 1162w; 1123w; 1111w; 1056w; 1023m; 927w; 753m; 674w.

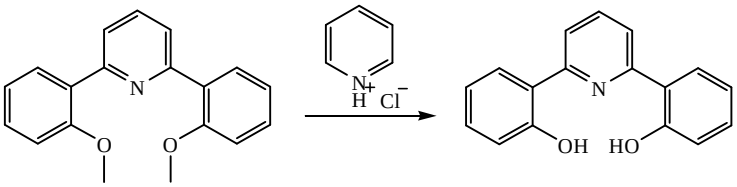
Mass spectrum (APCI) m/z (relative intensity): 320 $[M+H]^+$ (8%), 304 (M-15, $[C_{19}H_{14}NO_3]^+$) (20%), 290 (M-29, $[C_{19}H_{16}NO_2]^+$) (25%); 276 (M-43, $[C_{18}H_{14}NO_2]^+$) (89%); 261 (M-59, $[C_{18}H_{15}NO]^{\cdot +}$) (100%); 170 (M-149, $[C_{11}H_8NO]^+$) (12%); 135 (M-184, $[C_8H_7O_2]^+$) (15%).

Melting point: 68-70°C

High resolution mass spectrum (ES+, $M+H^+$): for $C_{20}H_{18}NO_3$, calculated: 320.1287, found: 320.1280.

IX. 4. 38. Preparation of 2,6-bis(2-hydroxyphenyl)pyridine

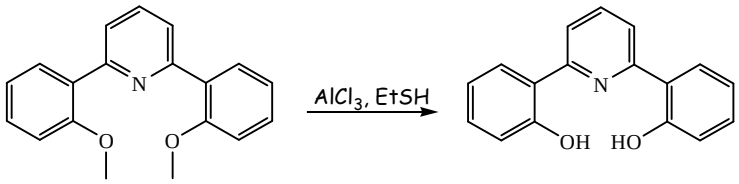
Procedure A:



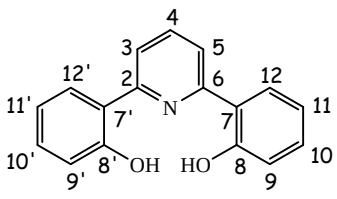
The substrate (2.01 g, 6.94 mmol, 1 eq.) and pyridinium hydrochloride (32 g, 277.50 mmol, 40 eq.) were placed in a one-necked, condenser-equipped flask (25 ml). The mixture was heated up to 210°C, where the mixture was melted. After 2 hours stirring at 210°C, it was let cool down to room temperature. Water was added and extraction was carried out with DCM. The combined organic layers was washed with water, dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column

chromatography using a 4 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.25) to obtain the title compound as a pure product (1.69 g, *93%* yield).

Procedure B:



Anhydrous $AlCl_3$ (82 mg, 0.60 mmol, 3 eq./OMe) was placed in a two-necked flask (10 ml), under argon. EtSH (1 ml) was added and the mixture was cooled down to 0°C. The substrate (30 mg, 0.10 mmol, 1 eq.) was added to the mixture and it was let warm up to room temperature. It gave a lemon coloured solution with precipitate in it. After overnight stirring, water was added, acidified to pH=1, extracted with DCM, dried over $MgSO_4$, filtered and evaporated to obtain the crude product (60 mg). The ^{1}H-NMR of the crude was very clean and showed complete conversion to the desired product. Flash column chromatography was carried out using a 4 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.25) to obtain the title compound as a pure product (17 mg, *64%* yield).



Registry number: 195813-56-0
Molecular formula: $C_{17}H_{13}NO_2$
Molecular weight: 263.29 g/mol
Physical aspect: white solid

^{1}H-NMR (500 MHz, $CDCl_3$)					^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	Mult.	J (Hz)	Int.	N°	δ (ppm)	N°
6.99	td	7.3, 1.0	2	11, 11’	117.95	9, 9’
7.05	dd	8.2, 0.8	2	9, 9’	119.79	3, 5
7.34	td	7.8, 1.6	2	10, 10’	120.04	11, 11’
7.67	dd	7.9, 1.6	2	12, 12’	121.58	7, 7’
7.69	d	8.0	2	3, 5	128.14	10, 10’
7.97	t	8.0	1	4	131.47	12, 12’
10.40	bs	-	2	OH	139.49	4
					156.10	2, 6
					156.53	8, 8’

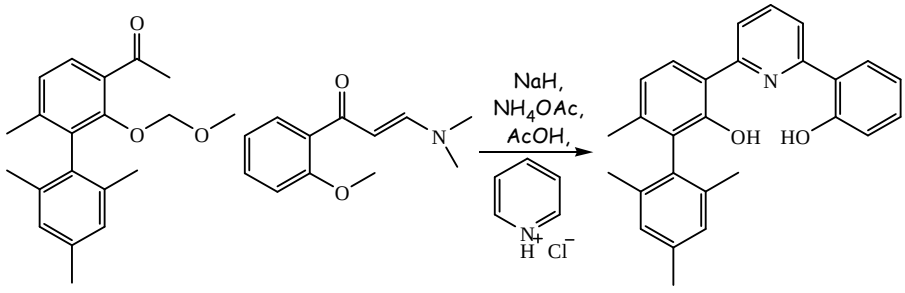
Infrared spectrum (film, cm^{-1}): 3226bs (O-H); 3045w, 2964w (C-H); 1614w, 1587s, 1487m (aromatic C-C); 1450m; 1384m; 1240w; 1186s (C-O); 1151m; 1118w; 1037w; 995w; 941w; 852w; 813m; 744w.

Mass spectrum (APCI) m/z (relative intensity): 264 $[M+H]^+$ (100%).

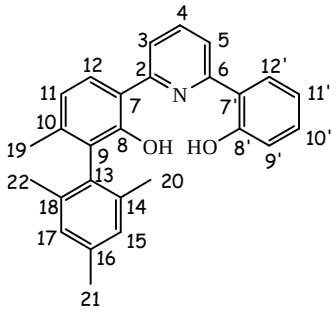
Melting point: 137-138°C

Elementary analysis: calculated: C: 77.55%, H: 4.98%, N: 5.32%; found: C: 77.68%, H: 4.62%, N: 5.24%.

IX. 4. 39. Preparation of 2-(6-(2-hydroxy-4-methyl-3-(2,4,6-trimethylphenyl)phenyl)pyridin-2-yl)phenol



NaH (80 mg, 60 w/w%, 2 mmol, 2 eq.) was suspended in dry, distilled THF (4 ml) in a two-necked flask (25 ml) under argon. The ketone (312 mg, 1 mmol, 1 eq.) dissolved in THF (2 ml) was added to the suspension dropwise. During this addition bubbling was observed. After 15 minutes stirring at room temperature, the enaminone (410 mg, 2 mmol, 2 eq.) dissolved in THF (2 ml) was added dropwise. The orange mixture was stirred at room temperature overnight. After a few hours some precipitation appeared in the solution. Then, glacial acetic acid (5 ml, 5 ml/mmol ketone) was added followed by ammonium acetate (770 mg, 10 mmol, 10 eq.). The mixture was refluxed at 110°C during 2 hours. Then it was let cool down to room temperature, concentrated on the vacuum pump and re-dissolved in DCM. It was washed with saturated aqueous solution of $NaHCO_3$, dried over Na_2SO_4, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 10 to 1 mixture of petrol ether and ethyl acetate as eluent to obtain the monodeprotected pure product (209 mg, *51%* yield). This compound was placed in a one-necked, condenser-equipped flask (10 ml). Pyridinium hydrochloride (2.36 g, 20.4 mmol, 40 eq.) was added and the mixture was heated up to 180°C for 3 hours. Then, it was let cool down to room temperature. Water was added and extraction was carried out with DCM. The combined organic layers was washed with water, dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 9 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.19) to obtain the title compound as a pure product (155 mg, *77%* yield for the deprotection and *39%* overall yield for the two steps).



Molecular formula: $C_{27}H_{25}NO_2$

Molecular weight: 395.49 g/mol

Physical aspect: white solid

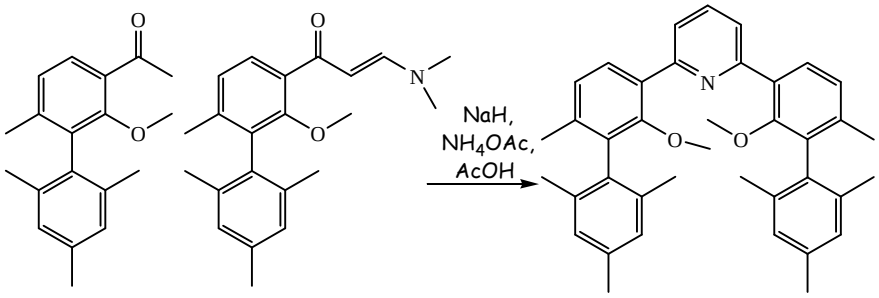
^{1}H-NMR (500 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.98	s	-	3	19
2.00	s	-	6	20, 22
2.34	s	-	3	21
6.93	dt	7.6, 0.9	1	11’
6.99	d	8.1	2	9’, 11
7.01	s	-	2	15, 17
7.29	dt	7.7, 1.5	1	10’
7.67	d	8.0	1	12’
7.73	dd	7.9, 2.9	2	3, 5
7.79	d	7.8	1	12
7.90	t	8.0	1	4

^{13}C-NMR (125 MHz, $CDCl_3$)	
δ (ppm)	N°
19.69	19
19.85	20, 22
21.15	21
117.93	9’
118.14	3
119.22	5
120.44	7
120.82	7’
121.09	11’
122.14	11
127.09	12
127.98	10’
128.03	9
128.85	15, 17
130.96	13
131.24	12’
137.23	14, 18
137.84, 139.40	10, 16
138.45	4
151.62	8
154.87	2
156.63	6
158.26	8’

Infrared spectrum (film, cm^{-1}): 3500w (O-H); 2916w, 2880w (C-H); 1608m, 1593m (aromatic C-C); 1562s; 1456s; 1429m; 1284m; 1244m; 1178s (C-O); 1114w; 1035m; 908s; 852s; 802s; 754s; 732s.
Mass spectrum (APCI) m/z (relative intensity): 396 $[M+H]^+$ (100%).
Melting point: 78-80°C
High resolution mass spectrum (ES+, $M+H^+$): for $C_{27}H_{26}NO_2$, calculated: 396.1964, found: 396.1976.

IX. 4. 40. Preparation of 2,6-bis(2-methoxy-4-methyl-3-(2,4,6-trimethylphenyl)phenyl)pyridine

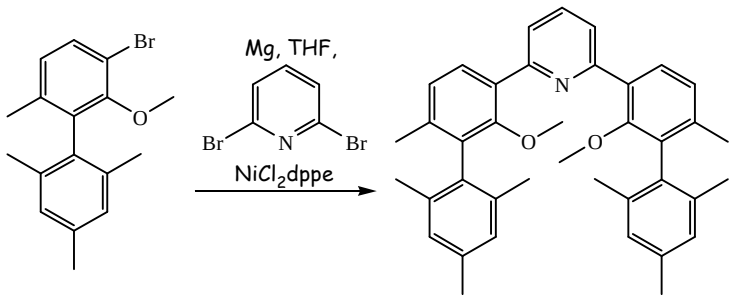
Procedure A:



NaH (40 mg, 60 w/w%, 1 mmol, 2 eq.) was suspended in dry, distilled THF (2 ml) in a two-necked flask (25 ml) under argon. The ketone (141 mg, 0.5 mmol, 1 eq.) dissolved in THF (1 ml) was added to the suspension dropwise. During the addition bubbling was observed. After 15 minutes stirring at room temperature, the enaminone (337 mg, 1 mmol, 2 eq.) was added dropwise. The orange mixture was stirred at room temperature during 36 hours. Precipitation did not occur, contrary to the other substrates. Then glacial acetic acid

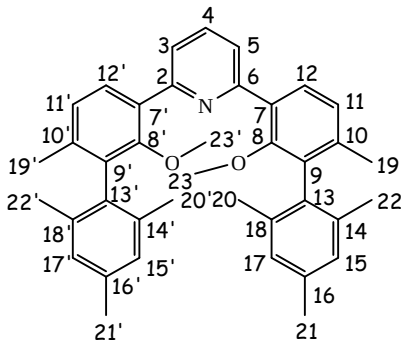
(2.5 ml, 5 ml/mmol ketone) was added followed by ammonium acetate (385 mg, 5 mmol, 10 eq.). The mixture was refluxed at 110°C during 2 hours. Then, it was let cool down to room temperature, concentrated on the vacuum pump and re-dissolved in DCM. It was washed with saturated aqueous solution of $NaHCO_3$, dried over Na_2SO_4, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 15 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.39) to obtain the title compound as a pure product (211 mg, *76%* yield).

Procedure B:



Magnesium powder (195 mg, 8.03 mmol, 1 eq.) was placed in a two-necked, flame-dried flask (25 ml) under argon. Dry, distilled THF (4 ml) was added followed by the dropwise addition of the bromide (2.56 g, 8.03 mmol, 1 eq.) dissolved in THF (8 ml). The mixture was stirred 3 hours at room temperature to obtain a grey solution. Meantime, 2,6-dibromopyridine (951 mg, 4.01 mmol, 0.5 eq.) and $NiCl_2$dppe (141 mg, 0.27 mmol, 3.3 mol%) were placed in a condenser-equipped, dry, two-necked flask (50 ml), under argon. Dry, freshly distilled THF (11 ml) was added and it was cooled down to

0°C. The previously prepared magnesium reagent was added dropwise. After 30 minutes stirring at 0°C, it was let warm up to room temperature and stirred overnight. White precipitate appeared in the orange solution. It was quenched by the addition of saturated NH_4Cl solution, extracted with DCM, dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 19 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.29) to obtain the title compound as a pure product (1.77 g, *80%* yield).



Molecular formula: $C_{39}H_{41}NO_2$
Molecular weight: 555.75 g/mol
Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.97	s	-	6	19, 19’
2.02	s	-	12	20, 20’, 22, 22’
2.34	s	-	6	21, 21’
3.24	s	-	6	23, 23’
6.96	s	-	4	15, 15’, 17, 17’
7.19	d	7.9	2	11, 11’
7.69	dd	8.5, 6.9	1	4
7.81	d	7.6	2	3, 5
7.88	d	7.9	2	12, 12’

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
19.55	19, 19’
20.25	20, 20’, 22, 22’
21.13	21, 21’
60.36	23, 23’
122.51	3, 5
126.03	11, 11’
128.11	15, 15’, 17, 17’
130.12	12, 12’
135.96	14, 14’, 18, 18’
131.37, 134.10, 134.33, 136.03, 136.40, 138.55	4, 7, 7’, 9, 9’, 10, 10’, 13, 13’, 16, 16’
155.39	2, 6
156.09	8, 8’

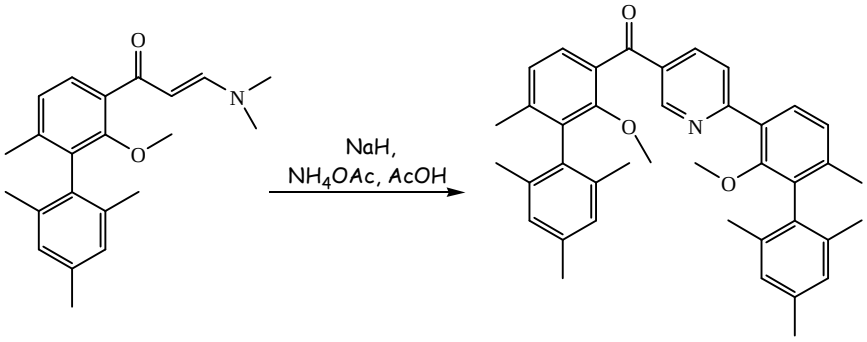
Infrared spectrum (film, cm^{-1}): 2918w (C-H); 1583m, 1560m (aromatic C-C); 1446s; 1361m; 1240s; 1051s (C-O); 921m; 852m; 811s; 734s.

Mass spectrum (APCI) m/z (relative intensity): 556 $[M+H]^+$ (100%).

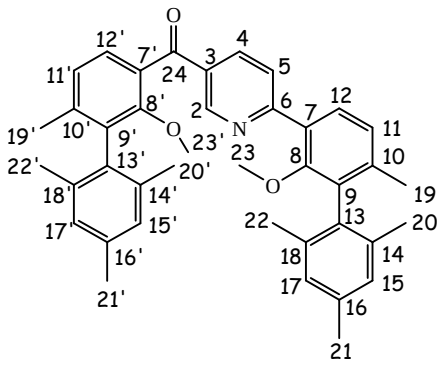
Melting point: 230-231°C

High resolution mass spectrum (ES+, $M+H^+$): for $C_{39}H_{42}NO_2$, calculated: 556.3216, found: 556.3235.

In procedure A ***(2-methoxy-4-methyl-3-(2,4,6-trimethylphenyl)phe-nyl)(6-(2-methoxy-4-methyl-3-(2,4,6-trimethyl-phenyl)phenyl)pyridin-3-yl)methanone*** formed as byproduct from the combination of two enaminone molecules:



This byproduct was purified by flash column chromatography using a 15 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.15).



Molecular formula: $C_{40}H_{41}NO_3$

Molecular weight: 583.76 g/mol

Physical aspect: yellow solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.97	s	-	3	19
2.00	s	-	6	20', 22'
2.01	s	-	9	19', 20, 22
2.32	s	-	3	21'
2.34	s	-	3	21
3.18	s	-	3	23'
3.20	s	-	3	23
6.95	s	-	2	15', 17'
6.96	s	-	2	15, 17
7.19	d	7.8	2	11, 11'
7.41	d	7.8	1	12'
7.75	d	7.9	1	12
8.00	dd	8.4, 0.7	1	5
8.14	dd	8.3, 2.3	1	4
9.05	dd	2.2, 0.7	1	2

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
19.58 19.77	19 19'
20.17	20, 20' 22, 22'
21.07 21.09	21 21'
60.43	23'
61.13	23
123.97	11'
125.64	11
126.19	5
128.15 128.27	15, 15' 17, 17'
128.58	12
129.98*	3, 12'
130.14	7'
131.11 132.78 133.62 134.28 134.59 136.58 136.66 136.93 139.93 142.26	4, 7, 9, 9', 10, 10', 13, 13', 16, 16'
135.83 135.86	14, 14' 18, 18'
151.11	2
155.61 155.67	8, 8'
160.12	6
195.41	24

*overlapping of the two peaks

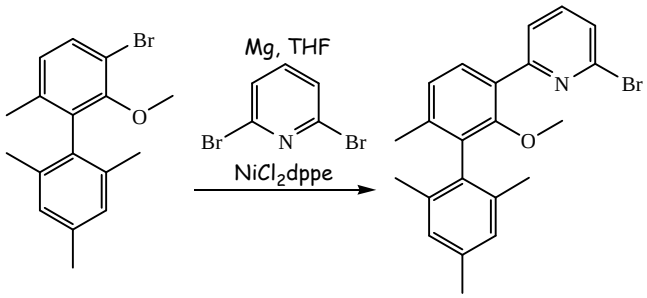
Infrared spectrum (film, cm^{-1}): 2920m, 2856w (C-H); 1662s (C=O); 1585s; 1454m; 1392m; 1294m; 1245m; 1051s (C-O); 910m; 850m; 796w; 730s.

Mass spectrum (APCI) m/z (relative intensity): 584 $[M+H]^+$ (100%).

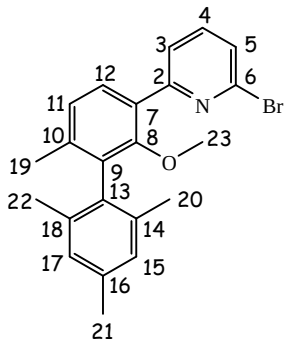
Melting point: 145-147°C

High resolution mass spectrum (ES+, M+H): for $C_{40}H_{42}O_3N$, calculated: 584.3165, found: 584.3171.

In procedure B a few % of ***2-bromo-6-(2-methoxy-4-methyl-3-(2,4,6-trimethylphenyl)phenyl)pyridine*** formed as byproduct:



This byproduct was purified by flash column chromatography using a 40 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.20), then by normal column chromatography using DCM as eluent (R_f = 0.78).



Molecular formula: $C_{22}H_{22}BrNO$

Molecular weight: 396.32 g/mol

Physical aspect: white solid

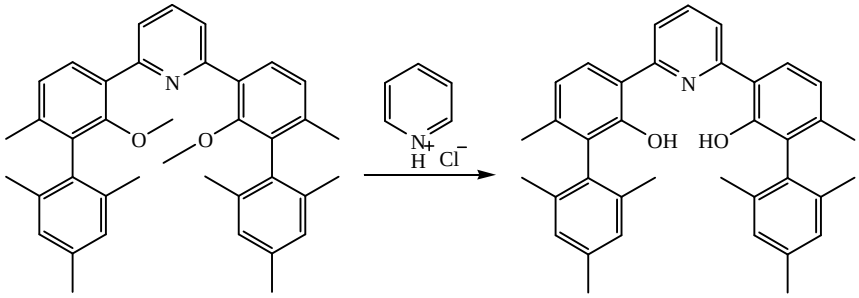
^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.96	s	-	3	19
1.99	s	-	6	20, 22
2.34	s	-	3	21
3.21	s	-	3	23
6.96	s	-	2	15, 17
7.17	d	7.9	1	11
7.39	dd	7.8, 0.8	1	5
7.54	t	7.8	1	4
7.72	d	7.9	1	12
7.87	dd	7.7, 0.8	1	3

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
19.57	19
20.20	20, 22
21.12	21
60.39	23
123.31	3
125.78	5
126.19	11
128.15	15, 17
129.51	7
129.97	12
135.91	14, 18
138.36	4
133.68, 134.52, 136.59, 139.63, 141.53	6, 9, 10, 13, 16
155.30	2
157.73	8

Infrared spectrum (film, cm^{-1}): 2918w, 2854w (C-H); 1575m, 1546m (aromatic C-C); 1425s; 1371m; 1245m; 1120m; 1053m; 796m.
Mass spectrum (APCI) m/z (relative intensity): 398 and 396 $[M+H]^+$ (100%), 368 and 366 (M-29, $[C_{20}H_{17}BrNO]^+$) (65%).
Melting point: 95-97°C
High resolution mass spectrum (ES+, $M+H^+$): for $C_{22}H_{23}OBrN$, ^{79}Br: calculated: 396.0963, found: 396.0966, ^{81}Br: found: 398.0973.

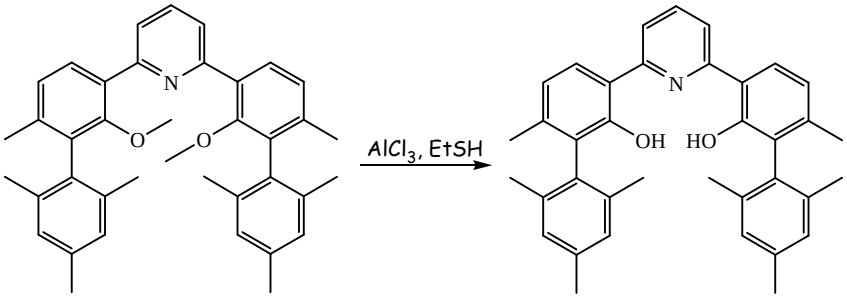
IX. 4. 41. Preparation of 2,6-bis(2-hydroxy-4-methyl-3-(2,4,6-trimethylphenyl)phenyl)pyridine

Procedure A:

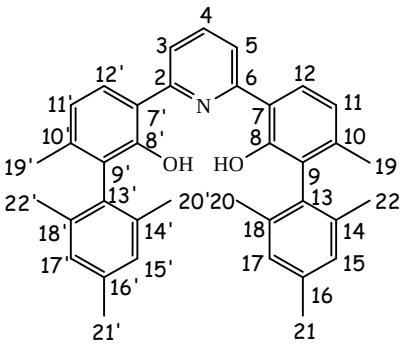


The substrate (203 mg, 0.37 mmol, 1 eq.) and pyridinium hydrochloride (1.69 g, 14.6 mmol, 40 eq.) were placed in a one-necked, condenser-equipped flask (25 ml). The mixture was heated up to 210°C, where the mixture was melted. After 2 hours stirring at 210°C, it was let cool down to room temperature. Water was added and extraction was carried out with DCM. The combined organic layers was washed with water, dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 10 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.26) to obtain the title compound as a pure product (178 mg, *92%* yield).

Procedure B:



Anhydrous $AlCl_3$ (200 mg, 1.5 mmol, 3 eq./OMe) was placed in a two-necked flask (10 ml), under argon. EtSH (2.5 ml) was added and the mixture was cooled down to 0°C. The substrate (139 mg, 0.25 mmol, 1 eq.) was added to the mixture and it was let warm up to room temperature. An orange coloured clear solution was obtained. After overnight stirring, water was added, acidified to pH=1, extracted with DCM, dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 10 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.37) to obtain the title compound as a pure product (116 mg, *88%* yield).



Molecular formula: $C_{37}H_{37}NO_2$
Molecular weight: 527.70 g/mol
Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.97	s	-	6	19, 19’
2.01	s	-	12	20, 20’, 22, 22’
2.36	s	-	6	21, 21’
6.93	d	7.7	2	11, 11’
7.01	s	-	4	15, 15’, 17, 17’
7.71	d	7.7	2	12, 12’
7.76-7.88	m	-	3	3, 4, 5

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
19.68	19, 19’
19.87	20, 20’, 22, 22’
21.18	21, 21’
119.58	3, 5
119.75	7, 7’
121.46	11, 11’
127.16	12, 12’
128.16	9, 9’
128.59	15, 15’, 17, 17’
132.08	13, 13’
136.98	14, 14’, 18, 18’
137.29, 137.50	16, 16’, 10, 10’
139.18	4
153.34	8, 8’
155.67	2, 6

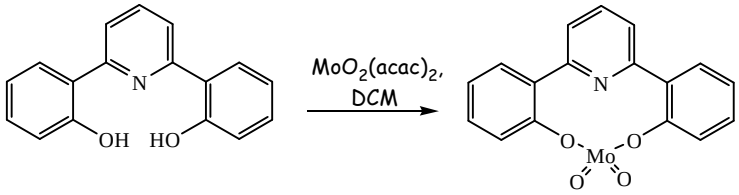
Infrared spectrum (film, cm^{-1}): 3498bs (O-H); 2945w, 2916w (C-H); 1610m, 1579m, 1560m (aromatic C-C); 1433m; 1244m; 1176m; 1116w; 1035w; 852m; 792s; 734m.

Mass spectrum (APCI) m/z (relative intensity): 528 $[M+H]^+$ (100%).

Melting point: 136-139°C

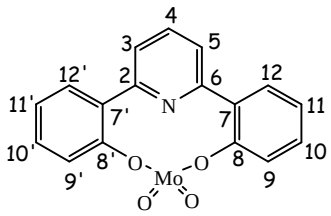
High resolution mass spectrum (ES+, $M+H^+$): for $C_{37}H_{38}NO_2$, calculated: 528.2903, found: 528.2886.

IX. 4. 42. Preparation of dioxomolybdenum (pyridin-2,6-diyl-bis(2-phenolate))



A mixture of the ligand (200 mg, 0.76 mmol 1 eq.) and $MoO_2(acac)_2$ (248 mg, 0.76 mmol, 1 eq.) was stirred in distilled, dry DCM (10 ml), at room temperature, during 24 hours. The forming orange precipitate was filtered off and washed with DCM to obtain the title compound as a pure product (244 mg, *82%* yield).

When it was necessary, the obtained complex could be purified from $MoO_2(acac)_2$ impurities by short refluxing in dichloromethane followed by precipitation of the partially dissolved complex with pentane, and filtration.



Registry number: 496924-77-7
Molecular formula: $C_{17}H_{11}MoNO_4$
Molecular weight: 389.21 g/mol
Physical aspect: orange solid

^{1}H-NMR (300 MHz, d-DMSO)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
6.96	d	7.8	2	9, 9’
7.04	t	7.6	2	11, 11’
7.42	t	7.2	2	10, 10’
7.98	d	7.3	2	12, 12’
8.14-8.30	m	-	3	3, 4, 5

^{13}C-NMR (125MHz, d-DMSO)	
δ (ppm)	N°
118.55	9, 9’
120.34	3, 5
123.28	11, 11’
126.19	7, 7’
129.41	10, 10’
131.05	12, 12’
139.88	4
153.30	2, 6
163.31	8, 8’

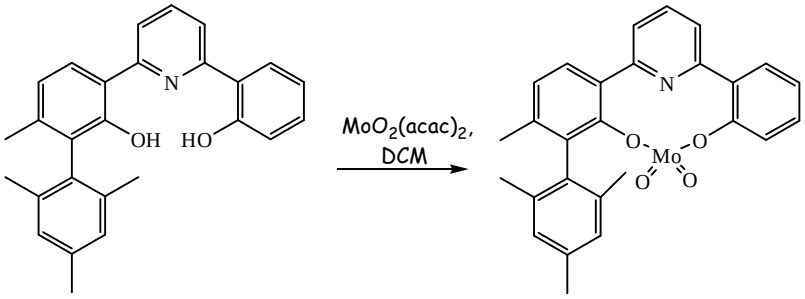
Infrared spectrum (KBr, cm^{-1}): 3112w, 3049w (C-H); 1595m, 1581m, 1558m (aromatic C-C); 1483w; 1446s; 1375w; 1288m; 1255m; 1236s; 1124m; 1037w; 939s (Mo=O); 881w; 865w; 815s; 759s.

Mass spectrum (APCI) m/z (relative intensity): 392 $[M+H]^+$ (20%), 376 (M-15, $[C_{17}H_{12}MoNO_3]^+$) (12%), 264 (M-127, $[C_{17}H_{14}NO_2]^+$) (100%).

Melting point: degradation > 270°C

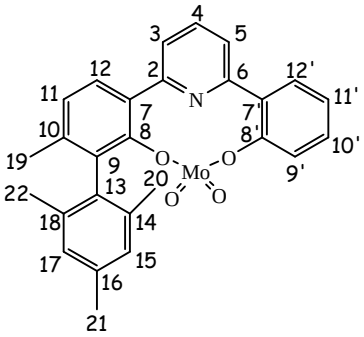
High resolution mass spectrum (ES+, $M+H^+$): for $C_{17}H_{12}NO_4Mo$, calculated: 391.9836, found: 391.9714. (The highest molecular peak, corresponding to Mo^{98}, the most abundant molybdenum isotope, was chosen for the interpretation.)

IX. 4. 43. Preparation of dioxomolybdenum (pyridin-2-yl-(4-methyl-3-(2,4,6-trimethylphenyl)-2-phenolate)-6-yl-(2-phenolate))



A mixture of the ligand (198 mg, 0.5 mmol 1 eq.) and $MoO_2(acac)_2$ (163 mg, 0.5 mmol, 1 eq.) was stirred in distilled, dry DCM (6.5 ml), at room temperature, during 2 days. The forming orange precipitate was filtered off and washed with DCM to obtain the title compound as a pure product (196 mg, *75%* yield).

When it was necessary, the obtained complex could be purified from $MoO_2(acac)_2$ impurities by short refluxing in dichloromethane followed by precipitation of the partially dissolved complex with pentane, and filtration.



Molecular formula: $C_{27}H_{23}MoNO_4$

Molecular weight: 521.42 g/mol

Physical aspect: pale orange solid

^{1}H-NMR (500 MHz, d-DMSO)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.88	s	-	3	19
1.95	s	-	6	20, 22
2.26	s	-	3	21
6.89-6.94	m	-	3	9', 15, 17
6.96-7.05	m	-	2	11, 11'
7.37	t	7.7	1	10'
7.89	d	7.9	1	12
7.94	d	8.1	1	12'
8.12	d	7.4	1	5
8.20-8.30	m	-	2	3, 4

^{13}C-NMR (125MHz, d-MeOH)	
δ (ppm)	N°
19.83	19
20.45	20, 22
21.29	21
26.79	MeOH*
104.22	9'
120.55	5
121.66	3
123.71, 123.82, 124.29, 125.71, 127.49	7, 7', 9, 11, 11'
128.91	10'
129.09	15, 17
130.44	12
132.27	12'
135.07, 137.23, 137.41, 140.72, 141.35	4, 10, 13, 14, 16, 18
155.21, 155.73	2, 6
161.60, 162.07	8, 8'

*broad signal of the coordinated d-MeOH

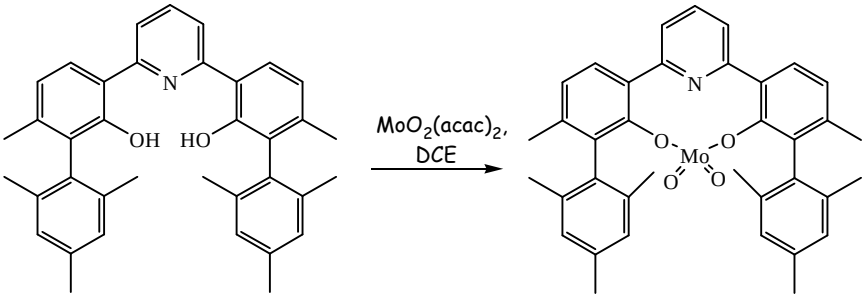
Infrared spectrum (KBr, cm^{-1}): 3018w, 2914w, 2852w (C-H); 1596m, 1577m (aromatic C-C); 1448m; 1365m; 1290m; 1257m; 1222w; 1199w; 1122w; 1037w; 956s, 916s (Mo=O); 904m; 806m; 767m; 752w.

Mass spectrum (APCI) m/z (relative intensity): 524 $[M+H]^+$ (12%), 508 (M-15, $[C_{26}H_{20}MoNO_4]^+$) (4%), 396 (M-127, $[C_{27}H_{26}NO_2]^+$) (100%).

Melting point: degradation > 300°C

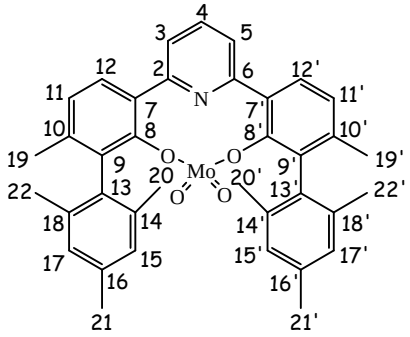
High resolution mass spectrum (ES+, $M+Na^+$): for $C_{27}H_{23}NO_4MoNa$, calculated: 546.0579, found: 546.0577. (The highest molecular peak, corresponding to Mo^{98}, the most abundant molybdenum isotope, was chosen for the interpretation.)

IX. 4. 44. Preparation of dioxomolybdenum (pyridin-2,6-diyl-bis(4-methyl-3-(2,4,6-trimethylphenyl)-2-phenolate))



A mixture of the ligand (200 mg, 0.38 mmol 1 eq.) and $MoO_2(acac)_2$ (123 mg, 0.38 mmol, 1 eq.) was stirred in distilled, dry DCE (2 ml), at 50°C, during 24 hours. The forming orange precipitate was filtered off and washed with DCM to obtain the title compound as a pure product (138 mg). The filtrate was evaporated, and the residue was washed with petroleum ether and DCM to obtain some additional pure product (additional 35 mg, *70%* overall yield).

When it was necessary, the obtained complex could be purified from $MoO_2(acac)_2$ impurities by short refluxing in dichloromethane followed by precipitation of the partially dissolved complex with pentane, and filtration.



Molecular formula:

$C_{37}H_{35}MoNO_4$

Molecular weight: 653.62 g/mol

Physical aspect: pale orange solid

^{1}H-NMR (300 MHz, d-DMSO)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.86	s	-	6	19, 19’
1.90	s	-	12	20, 20’, 22, 22’
2.25	s	-	6	21, 21’
6.86	s	-	4	15, 15’, 17, 17’
6.98	d	8.2	2	11, 11’
7.85	d	8.2	2	12, 12’
8.12-8.28	m	-	3	3, 4, 5

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
19.22	19, 19’
19.82	20, 20’, 22, 22’
20.73	21, 21’
121.58	3, 5
122.63	7, 7’
123.84	11, 11’
127.56	9, 9’
127.71	15, 15’, 17, 17’
129.47	12, 12’
133.93	13, 13’
135.29, 135.53	10, 10’, 14, 14’, 16, 16’, 18, 18’
138.77	4
153.58	2, 6
160.55	8, 8’

Infrared spectrum (KBr, cm^{-1}): 2916w, 2880w (C-H); 1600m, 1573m (aromatic C-C); 1437m; 1394m; 1280m; 1249s; 1203w;

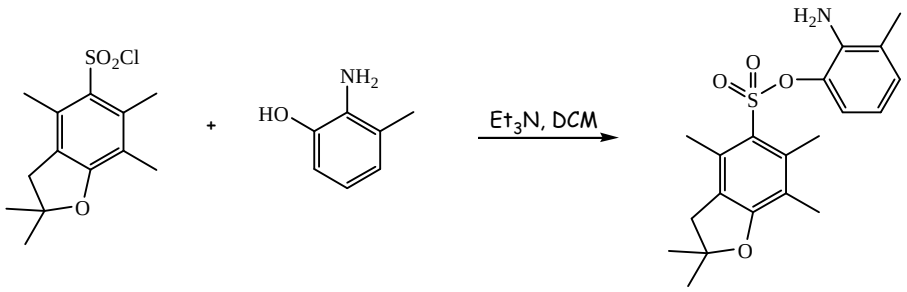
1189w; 1114w; 1058w; 1035w; 954s, 929s (Mo=O); 847m; 802s; 777w; 758w.

Mass spectrum (APCI) m/z (relative intensity): 656 $[M+H]^+$ (50%), 640 (M-15, $[C_{36}H_{32}MoNO_4]^+$) (3%), 528 (M-127, $[C_{37}H_{38}NO_2]^+$) (100%).

Melting point: degradation > 300°C

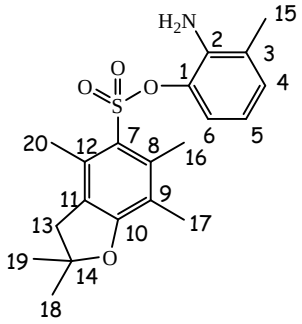
High resolution mass spectrum (ES+, $M+H^+$): for $C_{37}H_{36}NO_4Mo$, calculated: 656.1712, found: 656.1698. (The highest molecular peak, corresponding to Mo^{98}, the most abundant molybdenum isotope, was chosen for the interpretation.)

IX. 4. 45. Preparation of 2-amino-3-methylphenyl 2,3-dihydro-2,2,4, 6,7-pentamethylbenzofuran-5-sulfonate



2-Amino-3-methylphenol (1.24 g, 10 mmol, 1 eq.) was dissolved in DCM (25 ml) in a one-necked flask (100 ml). Triethylamine (1.39 ml, 10 mmol, 1 eq.) was added to the solution. Then the mixture was cooled down to 0°C and 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl chloride (2.89 g, 10 mmol, 1 eq.) was added to it. The reaction mixture was let warm up to room temperature. After 2 hours stirring at room temperature, the reaction was complete, based on TLC. Water was added and the separated organic phase was washed with brine, dried over $MgSO_4$, filtered and

evaporated. The red-brown crude product was purified by flash column chromatography using a 3 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.63) to obtain the title compound as a pure product (3.24 g, *86%* yield).



Molecular formula: $C_{20}H_{25}NO_4S$

Molecular weight: 375.48 g/mol

Physical aspect: light brown solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.50	s	-	6	18, 19
2.15	s	-	3	17
2.18	s	-	3	15
2.37	s	-	3	16
2.58	s	-	3	20
2.98	s	-	2	13
3.80	bs	-	2	NH_2
6.41-6.50	m	-	2	5, 6
6.88-6.93	m	-	1	4

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
12.47	17
17.46	16
17.96	20
19.15	15
28.47	18, 19
42.87	13
87.32	14
117.18	6
119.63	5
128.42	4
118.31, 124.57, 125.26, 125.67, 134.99, 136.93, 138.57, 140,83	1, 2, 3, 7, 8, 9, 11, 12
160.74	10

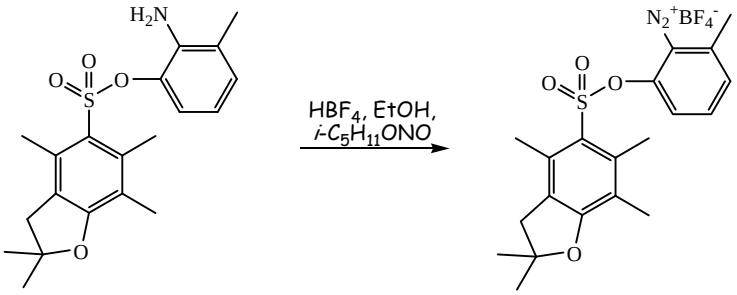
Infrared spectrum (film, cm^{-1}): 3483w, 3394w (N-H); 2975w, 2931w (C-H); 1625m (NH_2); 1577m, 1483m (aromatic C-C); 1456w; 1353m (S=O); 1288w; 1176s (S=O); 1147w; 1091s (C-O); 916s (S-O); 804m; 781m; 752m.

Mass spectrum (APCI) m/z (relative intensity): 376 $[M+H]^+$ (100%), 253 (M-122, $[C_{13}H_{17}O_3S]^+$) (82%) 189 (M-186, $[C_{13}H_{17}O]^+$) (25%), 122 (M-253, $[C_7H_8NO]^+$) (26%).

Melting point: 134-137°C

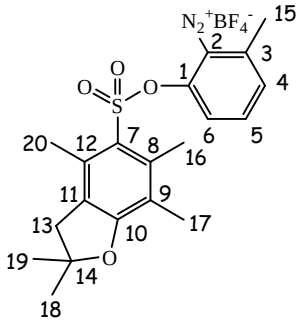
High resolution mass spectrum (ES+, $M+H^+$): for $C_{20}H_{26}NO_4S$, calculated: 376.1583, found: 376.1583.

IX. 4. 46. Preparation of 2-diazo-3-methylphenyl (2,3-dihydro-2,2,4, 6,7-pentamethylbenzofuran-5-sulfonate) tetrafluoroborate



Ethanol (30 ml) was placed in a one-necked flask (100 ml). It was cooled down to 0°C and HBF_4 (2.5 ml, 54% in diethyl ether, 18 mmol, 3 eq.) was added to it followed by the sulfonate (2.30 g, 6.1 mmol, 1 eq.). The resulted dark brown mixture was treated dropwise by isoamyl nitrite (1.4 ml, 11 mmol, 1.8 eq.). In 1 hour, considerable amount of yellow precipitate formed. Diethyl ether (10 ml) was added to dilute the mixture and it was stirred for an additional 1 hour at 0°C. Then the precipitate was filtered off and washed with cold water and

diethyl ether several times. The water content of the resulted product can be eliminated by freeze-drying, but this long process is unnecessary for the next step of the synthesis. Global yield will be given for the two steps.



Molecular formula: $C_{20}H_{23}SO_4N_2^+BF_4^-$

Molecular weight: 474.28 g/mol

Physical aspect: light yellow solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.51	s	-	6	18, 19
2.15	s	-	3	17
2.43	s	-	3	16
2.57	s	-	3	20
2.79	s	-	3	15
3.03	s	-	2	13
7.25	d	-*	1	6
7.52	d	7.9	1	4
7.98	t	8.3	1	5

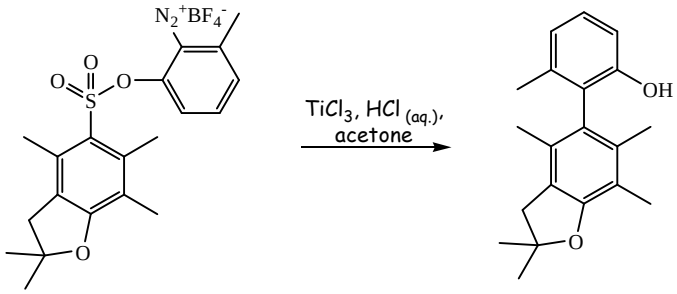
*Due to an extensive overlap with the signal of $CHCl_3$, this coupling constant could not be accurately measured.

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
12.47	17
18.02	16
18.96	20
19.22	15
28.50	18, 19
42.53	13
88.45	14
108.53	2
121.19	6
129.99	4
142.81	5
119.45, 121.96, 126.55, 135.98, 142.05, 147.67	3, 7, 8, 9, 11, 12
151.00	1
162.55	10

Infrared spectrum (film, cm^{-1}): 2975w, 2933w (C-H); 2270m (N_2^+); 1596w, 1571m, 1481m (aromatic C-C); 1371s (S=O); 1292m; 1261m; 1211w; 1178s (S=O); 1091m; 1058m; 1035m; 962m; 914m; 850w; 802m.

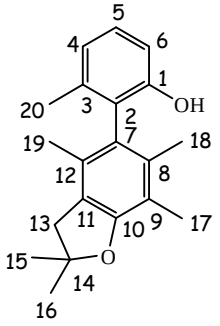
Mass spectrum (APCI) m/z (relative intensity): M'=M-BF_4^-, 387 $[M'+H]^+$ (6%), 323 (M'-64, $[C_{20}H_{23}N_2O_2]^+$) (33%), 190 (M'-197, $[C_{13}H_{18}O]^{\cdot +}$) (100%).

IX. 4. 47. Preparation of 2-(2,3-dihydro-2,2,4,6,7-pentamethylbenzo-furan-5-yl)-3-methylphenol



The crude product of the previous reaction was dissolved in acetone (12 ml) in a one-necked flask (50 ml) at 0°C. The solution was treated dropwise with $TiCl_3$ (4.5 ml, 30 w/w% in 2 N HCl; 8.8 mmol). The dark blue colour of the $TiCl_3$ solution disappeared on the addition and gas evolution was observed. The formed gases were evacuated from the flask through a needle. After the addition of the total amount of $TiCl_3$ the dark blue colour stayed and the gas evolution was ceased in 30 minutes. The mixture was diluted with water and extracted with DCM. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated. The brown crude product was purified by flash column chromatography using a 20 to 1

mixture of petrol ether and ethyl acetate as eluent (R_f = 0.32) to obtain the title compound as a pure product (1.29 g, *71%* overall yield for the 2 steps).



Molecular formula: $C_{20}H_{24}O_2$

Molecular weight: 296.40 g/mol

Physical aspect: white solid

^{1}H-NMR (500 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.51, 1.52	2 s	-	6	15, 16
1.79	s	-	3	18
1.85	s	-	3	19
1.92	s	-	3	20
2.14	s	-	3	17
2.97	s	-	2	13
4.63	s	-	1	OH
6.84	t	8.2	2	4, 6
7.16	t	8.0	1	5

^{13}C-NMR (125 MHz, $CDCl_3$)	
δ (ppm)	N°
12.29	17
16.11	18
16.47	19
19.73	20
28.65, 28.74	15, 16
42.83	13
85.82	14
111.86	6
116.28, 123.74, 124.16, 127.06, 131.15, 136.23, 137.81	2, 3, 7, 8, 9, 11, 12
121.65	4
127.99	5
152.92	1
157.32	10

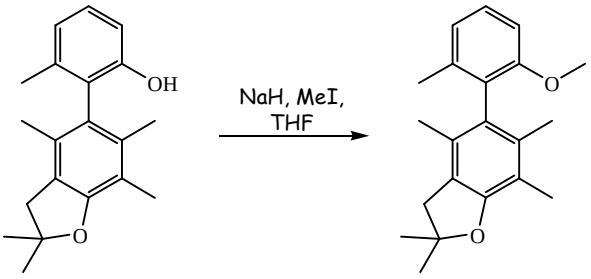
Infrared spectrum (film, cm^{-1}): 3515bs (OH); 2970m, 2920m (C-H); 1595m, 1573m (aromatic C-C); 1460s; 1367w; 1340w; 1278s (C-O); 1255w; 1186m; 1085s (C-O); 852m; 779s; 750w.

Mass spectrum (APCI) m/z (relative intensity): 297 $[M+H]^+$ (100%), 242 (M-54, $[C_{16}H_{18}O_2]^{\cdot +}$) (8%).

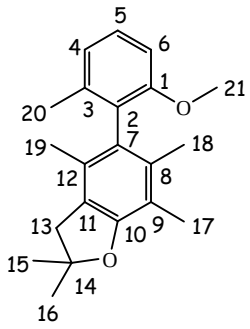
Melting point: 122-125°C

High resolution mass spectrum (ES+, $M+H^+$): for $C_{20}H_{25}O_2$, calculated: 297.1855, found: 297.1854.

IX. 4. 48. Preparation of 2,3-dihydro-5-(2-methoxy-6-methylphenyl)-2,2,4,6,7-pentamethylbenzofuran



NaH (15 mg, 60 w/w%, 0.38 mmol, 1.1 eq.) and dried, freshly distilled THF (0.7 ml) were placed in a flame-dried, two-necked flask (25 ml) under argon. Subsequently, the substrate (100 mg, 0.34 mmol, 1 eq.) was added in one portion. After 30 min stirring at room temperature, MeI (25 µl, 0.4 mmol, 1.1 eq.) was added dropwise. After a few hours stirring, the reaction was quenched by water and extracted with DCM. The organic phase was dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 20 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.34) to obtain the title compound as a pure product (98 mg, *94%* yield).



Molecular formula: $C_{21}H_{26}O_2$

Molecular weight: 310.43 g/mol

Physical aspect: white solid

^{1}H-NMR (500 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.49, 1.50	2 s	-	6	15, 16
1.74	s	-	3	18
1.80	s	-	3	19
1.87	s	-	3	20
2.13	s	-	3	17
2.94	d	15.1	1	13a
2.98	d	15.1	1	13b
3.69	s	-	3	21
6.80	d	8.2	1	6
6.89	d	7.5	1	4
7.21	t	7.9	1	5

^{13}C-NMR (125 MHz, $CDCl_3$)	
δ (ppm)	N°
12.86	17
16.68	18
17.05	19
20.20	20
29.23	15, 16
43.46	13
56.11	21
85.74	14
108.54	6
115.50, 122.96, 128.83, 129.98, 130.51, 134.71, 138.84	2, 3, 7, 8, 9, 11, 12
122.69	4
127.81	5
156.66	10
157.68	1

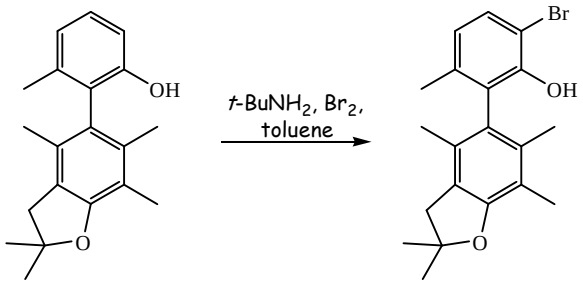
Infrared spectrum (film, cm^{-1}): 2970w, 2921m (C-H); 1595w, 1577m (aromatic C-C); 1465s; 1278w; 1255s, 1083s (C-O); 854w; 777m; 748w.

Mass spectrum (APCI) m/z (relative intensity): 311 $[M+H]^+$ (100%), 255 (M-55, $[C_{17}H_{19}O_2]^+$) (20%).

Melting point: 72-75°C

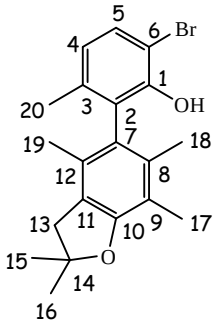
Elementary analysis: calculated: C: 81.25%, H: 8.44%; found: C: 80.79%, H: 8.50%.

IX. 4. 49. Preparation of 6-bromo-2-(2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-5-yl)-3-methylphenol



Dry, freshly distilled toluene (13 ml) and dry, freshly distilled *t*-$BuNH_2$ (2.80 ml, 26.4 mmol, 2 eq.) were placed in a two-necked, flame-dried flask (50 ml) under argon and cooled down to -30°C. Bromine (670 µl, 13 mmol, 1 eq.) was added dropwise. The reaction was kept between -30 and -10°C during 50 min. There was a little amount of orange solid in the obtained lemon yellow gel, so to help the reaction toluene (2 ml) was added. Then, it was cooled down to -78°C and the substrate (3.86 g, 13 mmol, 1 eq.) was added dropwise dissolved in DCM (3 ml). At the moment of the addition a yellow suspension was formed, which changed into an orange clear solution in a few minutes. The reaction was kept during 2 hours at -78°C and let warm to room temperature very slowly, over a period of 5 hours. The reaction was quenched by the addition of water, and then extracted with DCM. The organic layer was washed with saturated

$Na_2S_2O_3$ solution and brine, dried over Mg_2SO_4, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 20 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.31) to obtain the title compound as a pure product (3.57 g, *73%* yield).



Molecular formula: $C_{20}H_{23}BrO_2$

Molecular weight: 375.30 g/mol

Physical aspect: white solid

^{1}H-NMR (500 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.51	s	-	6	15, 16
1.77	s	-	3	18
1.84	s	-	3	19
1.87	s	-	3	20
2.14	s	-	3	17
2.97	s	-	2	13
5.11	s	-	1	OH
6.75	d	8.2	1	4
7.37	d	8.2	1	5

^{13}C-NMR (125 MHz, $CDCl_3$)	
δ (ppm)	N°
12.28	17
16.14	18
16.47	19
19.50	20
28.67, 28.71	15, 16
42.80	13
85.86	14
105.91	6
116.26, 123.71, 124.53, 128.60, 130.59, 135.66, 137.61	2, 3, 7, 8, 9, 11, 12
122.78	4
130.97	5
149.68	1
157.38	10

Infrared spectrum (film, cm^{-1}): 3494s (OH); 2972m, 2921m (C-H); 1595m, 1564w (aromatic C-C); 1448s; 1406s; 1278s (C-O); 1265w; 1182m; 1116m; 1085s (C-O); 1035m; 854m; 794m.

Mass spectrum (APCI) m/z (relative intensity): 377 and 375 $[M+H]^+$ (94%, 100%), 319 (M-56, $[C_{16}H_{16}BrO_2]^+$)(16%), 296 (M-79, $[C_{20}H_{24}O_2]^{\cdot +}$)(20%).

Melting point: 126-129°C

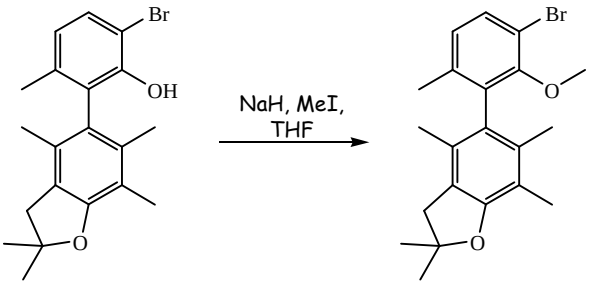
High resolution mass spectrum (ES+, M+Na): for $C_{20}H_{23}O_2BrNa$, ^{79}Br: calculated: 397.0779, found: 397.0791, ^{81}Br: found: 399.0784.

Separation of the enantiomers: MPLC, semi-preparative chiral AD column (20µm); 99.2 to 0.8 mixture of hexane and isopropanol as eluent; 70 ml per minute rate of solvent; 150 mg product per injection.

$[\alpha]^{D}_{20}$: -28.3 (0.035 M, $CHCl_3$) for the first fraction.

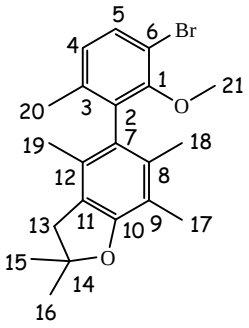
$[\alpha]^{D}_{20}$: +28.5 (0.053 M, $CHCl_3$) for the second fraction.

IX. 4. 50. Preparation of 5-(3-bromo-2-methoxy-6-methylphenyl)-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran



NaH (192 mg, 60 w/w%, mmol, 4.80 mmol, 1.1 eq.) and dry, freshly distilled THF (5 ml) were placed in a flame-dried, two-necked flask (25 ml) under argon. Subsequently, the substrate (1.64 g, 4.36 mmol, 1 eq.) was added dissolved in dry, distilled THF (4 ml). After 1 hour stirring at room temperature, MeI (300 µl, 4.82 mmol, 1.1 eq.)

was added dropwise. After a few hours stirring, the reaction was quenched by water and extracted with DCM. The organic phase was dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 30 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.28) to obtain the title compound as a pure product (1.39 g, *82%* yield).



Molecular formula: $C_{21}H_{25}BrO_2$

Molecular weight: 389.33 g/mol

Physical aspect: colourless oil

^{1}H-NMR (500 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.50	s	-	6	15, 16
1.77	s	-	3	18
1.84	s	-	3	19
1.86	s	-	3	20
2.13	s	-	3	17
2.96	s	-	2	13
3.42	s	-	3	21
6.92	d	8.2	1	4
7.42	d	8.2	1	5

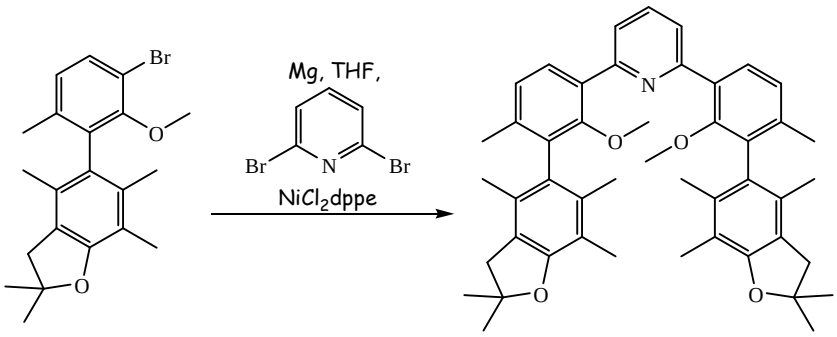
^{13}C-NMR (125 MHz, $CDCl_3$)	
δ (ppm)	N°
12.26	17
16.74	18
16.88	19
19.43	20
28.57, 28.61	15, 16
42.86	13
59.88	21
85.53	14
114.47, 115.20, 122.79, 127.70, 129.29, 134.07, 136.99, 138.35	2, 3, 6, 7, 8, 9, 11, 12
126.56	4
131.33	5
154.48	10
156.46	1

Infrared spectrum (film, cm^{-1}): 2970m, 2929m (C-H); 1596m (aromatic C-C); 1456s; 1392s; 1278s (C-O); 1263m; 1147w; 1124w; 1085s (C-O); 1054m; 856m; 802m; 725w.

Mass spectrum (APCI) m/z (relative intensity): 391 and 389 $[M+H]^+$, (98%, 100%); 333 (M-55, $[C_{17}H_{17}BrO_2]^+$)(22%); 310 (M-78, $[C_{21}H_{25}O_2]^{\cdot +}$) (32%); 254 (M-134, $[C_{17}H_{17}O_2]^{\cdot +}$) (10%).

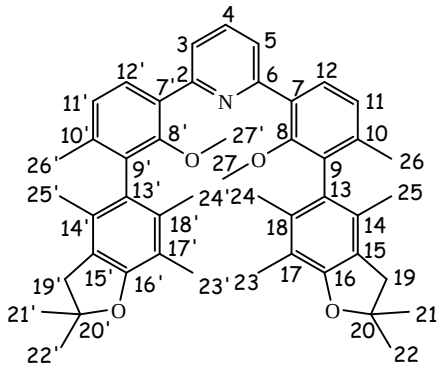
High resolution mass spectrum (ES+, $M+H^+$): for $C_{21}H_{26}O_2Br$, ^{79}Br: calculated: 389.1116, found: 389.1116, ^{81}Br: found: 391.1201.

IX. 4. 51. Preparation of 2,6-bis(3-(2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-5-yl)-2-methoxy-4-methylphenyl)pyridine



Magnesium powder (86 mg, 3.54 mmol, 1 eq.) was placed in a two-necked, condenser-equipped, flame-dried flask (25 ml) under argon. Dry, distilled THF (2 ml) was added followed by the dropwise addition of the bromide (1.37 g, 3.52 mmol, 1 eq.) dissolved in THF (3 ml). The mixture was gently heated to 45-50°C during 4 hours to obtain a grey solution. Meantime, 2,6-dibromopyridine (422 mg, 1.78 mmol, 0.5 eq.) and $NiCl_2$dppe (186 mg, 0.35 mmol, 10 mol%) were

placed in a condenser-equipped, dry, two-necked flask (25 ml), under argon. Dry, freshly distilled THF (4.4 ml) was added and it was cooled down to 0°C. The previously prepared, cooled magnesium reagent was added dropwise. After 20 minutes stirring at 0°C, it was let warm up to room temperature and stirred overnight. The orange colour of the mixture turned to dark green during the overnight stirring. The reaction was quenched by the addition of saturated NH_4Cl solution, extracted with DCM, dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 20 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.20) to obtain the title compound as a pure product (811 mg, *66%* yield).



Molecular formula: $C_{47}H_{53}NO_4$

Molecular weight: 695.93 g/mol

Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.50, 1.52	2 s	-	12	21, 21', 22, 22'
1.85	s	-	6	24, 24'
1.91	s	-	6	25, 25'
1.96	s	-	6	26, 26'
2.15	s	-	6	23, 23'
2.98	s	-	4	19, 19'
3.23	s	-	6	27, 27'
7.19	d	7.9	2	11, 11'
7.69	t	7.7	1	4
7.81	d	7.6	2	3, 5
7.87	d	7.9	2	12, 12'

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
12.33	23, 23'
16.82	24, 24'
17.04	25, 25'
19.83	26, 26'
28.61, 28.64	21, 21', 22, 22'
42.98	19, 19'
60.35	27, 27'
85.42	20, 20'
115.15, 122.52, 122.70, 125.85	3, 5, 7, 7', 11, 11', 12, 12'
128.49, 129.45, 129.84, 131.34, 134.26, 135.35, 135.93	9, 9', 10, 10', 13, 13', 14, 14', 15, 15', 17, 17', 18, 18'
139.40	4
155.84	2, 6
156.17	16, 16'
156.28	8, 8'

Infrared spectrum (film, cm^{-1}): 2970m, 2925m, 2864w (C-H); 1595m, 1583m, 1574m (aromatic C-C); 1442s; 1367m; 1276m; 1247m; 1085s (C-O); 1053w; 908m; 804m; 730s.

Mass spectrum (APCI) m/z (relative intensity): 696 $[M+H]^+$ (100%).

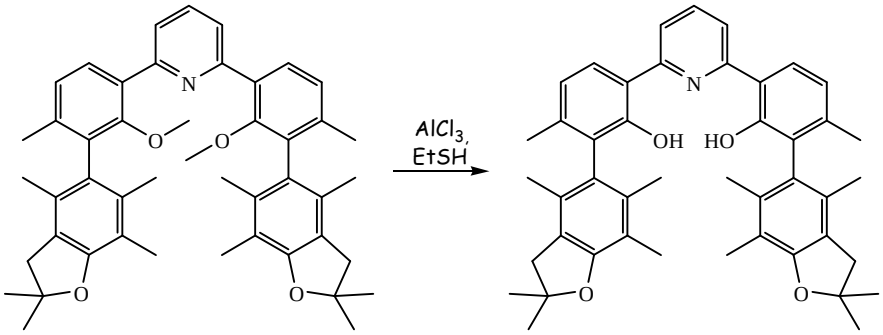
Melting point: 183-185°C

High resolution mass spectrum (ES+, $M+H^+$): for $C_{47}H_{54}NO_4$, calculated: 696.4053, found: 696.4049.

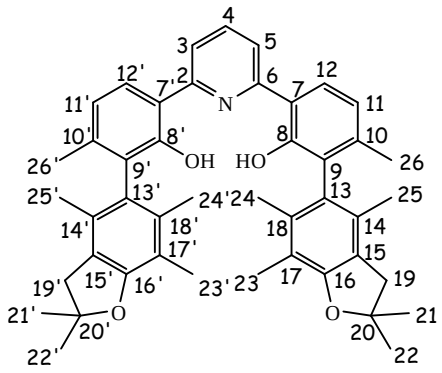
$[\alpha]^D_{21}$: -49.3 (0.014 M, DCM).

$[\alpha]^D_{21}$: +57.7 (0.015 M, DCM).

IX. 4. 52. Preparation of 2,6-bis(3-(2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-5-yl)-2-hydroxy-4-methylphenyl)pyridine



The substrate (140 mg, 0.2 mmol, 1 eq.) was dissolved in DCM (3 ml) in a dry, two-necked flask (10 ml) under argon. It was cooled down to 0°C and EtSH (2 ml) was added followed by anhydrous $AlCl_3$ (107 mg, 0.8 mmol, 2 eq./OMe). The orange mixture was let warm up to room temperature. After 2 hours stirring, water was added, the mixture was acidified to pH=1, extracted with DCM, dried over Na_2SO_4, filtered and evaporated to obtain the crude product (160 mg). On the basis of the ^{1}H-NMR, the crude contained mainly the desired compound and only a little amount of ring-opened byproduct. Flash column chromatography was carried out using DCM as eluent (R_f = 0.73) to obtain the title compound as a pure product (86 mg, *65%* yield).



Molecular formula: $C_{45}H_{49}NO_4$

Molecular weight: 667.87 g/mol

Physical aspect: white solid

^{1}H-NMR (500 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.51	s	-	12	21, 21', 22, 22'
1.82	s	-	6	24, 24'
1.89	s	-	6	25, 25'
1.93	s	-	6	26, 26'
2.15	s	-	6	23, 23'
2.98	s	-	4	19, 19'
6.90	d	8.1	2	11, 11'
7.69	d	8.1	2	12, 12'
7.75-7.85	m	-	3	3, 4, 5

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
12.35	23, 23'
16.23	24, 24'
16.60	25, 25'
19.94	26, 26'
28.74, 28.76	21, 21', 22, 22'
42.92	19, 19'
85.55	20, 20'
115.78, 119.59	7, 7', 17, 17',
119.50, 121.25	3, 5, 11, 11'
123.22, 126.09, 129.08, 130.49, 135.43, 137.36	9, 9', 10, 10', 13, 13', 14, 14', 15, 15', 18, 18'
126.95	12, 12'
139.91	4
153.85, 155.65, 156.89	2, 6, 8, 8', 16, 16'

Infrared spectrum (film, cm^{-1}): 3485w (OH); 2972w, 2921w, 2852w (C-H); 1579m, 1562m (aromatic C-C); 1454m; 1404m; 1276m; 1247m; 1085s (C-O); 908m; 792m; 730s.

Mass spectrum (APCI) m/z (relative intensity): 668 $[M+H]^+$ (100%).

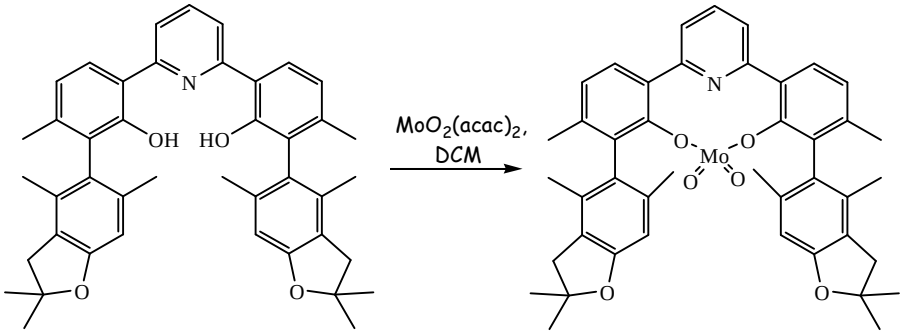
Melting point: 144-147°C

High resolution mass spectrum (ES+, $M+H^+$): for $C_{45}H_{50}NO_4$, calculated: 668.3740, found: 668.3734.

$[\alpha]^D_{22}$: - 69.4 (0.016 M, DCM).

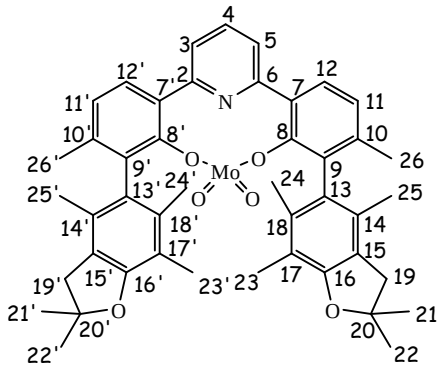
$[\alpha]^D_{21}$: + 95.7 (0.009 M, DCM).

IX. 4. 53. Preparation of dioxomolybdenum (pyridin-2,6-diyl-bis((2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-5-yl)-6-methyl-2-phenolate))



A mixture of the ligand (85 mg, 0.13 mmol, 1 eq.) and $MoO_2(acac)_2$ (21 mg, 0.06 mmol, 0.5 eq.) was stirred in distilled, dry DCM (2 ml), at room temperature, during 24 hours. The mixture was evaporated and put on the vacuum-pump for 1 hour. Then it was re-dissolved in DCM (2 ml) and stirred to an additional few hours. This

cycle was repeated until the complete conversion of $MoO_2(acac)_2$. Then, the evaporated residue was washed with petroleum ether in order to remove the residue of pentane-2,4-dione and the excess of the ligand. By this method, the title compound was obtained as a pure product (41 mg, *81%* overall yield).



Molecular formula: $C_{45}H_{47}MoNO_6$

Molecular weight: 793.80 g/mol

Physical aspect: pale orange solid

^{1}H-NMR (500 MHz, d-MeOH)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.48	s	-	6	21, 21', 22, 22'
1.49	s	-	6	
1.83	s	-	6	24, 24'
1.88	s	-	6	25, 25'
1.95	s	-	6	26, 26'
2.08	s	-	6	23, 23'
2.95	d	15.2	2	19a, 19'a, 19b, 19'b
3.00	d	15.2	2	
7.02	d	8.2	2	11, 11'
7.80	d	8.2	2	12, 12'
8.12	d	8.0	2	3, 5
8.21	t	8.0	1	4

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
12.34	23, 23'
16.84	24, 24'
17.03	25, 25'
20.02	26, 26'
28.95, 28.99	21, 21', 22, 22'
43.80	19, 19'
86.49	20, 20'
116.04, 123.77, 125.27	7, 7', 9, 9', 17, 17'
123.31, 123.79, 128.66	3, 5, 11, 11', 12, 12'
129.65, 130.88, 131.95, 135.57, 140.59, 142.05	4, 10, 10', 13, 13', 14, 14', 15, 15', 18, 18'
156.39	16, 16'
157.35	2, 6
161.68	8.8'

Infrared spectrum (KBr, cm^{-1}): 2968w, 2923m, 2852w (C-H); 1649w; 1596s, 1577m (aromatic C-C); 1446m; 1382w; 1278m; 1249w; 1085s (C-O); 958s (Mo=O); 794s.

Mass spectrum (APCI) m/z (relative intensity): 796 $[M+H]^+$ (14%), 668 (M-127, $[C_{45}H_{50}NO_4]^+$) (100%).

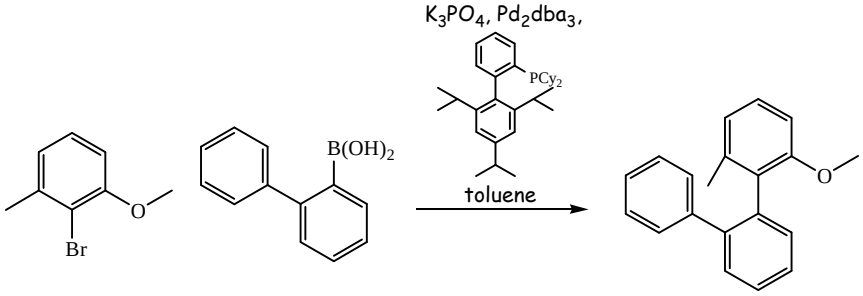
Melting point: degradation > 300°C

High resolution mass spectrum (ES+, $M+Na^+$): for $C_{45}H_{47}NO_6NaMo$, calculated: 818.2355, found: 818.2346. (The highest molecular peak, corresponding to Mo^{98}, the most abundant molybdenum isotope, was chosen for the interpretation.)

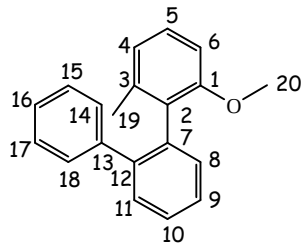
$[\alpha]^D_{22}$: - 109.8 (0.006 M, MeOH).

$[\alpha]^D_{21}$: + 124.2 (0.010 M, MeOH).

IX. 4. 54. Preparation of 1-methoxy-3-methyl-2-(2-phenyl-phenyl)-benzene



The boronic acid (2.97 g, 15 mmol, 2 eq.), the bromide (1.51 g, 7.5 mmol, 1 eq.), dry K_3PO_4 (4.77g, 22.5 mmol, 3 eq.), Pd_2dba_3 (69 mg, 0.075 mmol, 1 mol %) and X-Phos ligand (72 mg, 0.15 mmol, 2 mol %) were placed in a flame-dried Schlenk tube under argon. It was vacuumed and argon-filled three times. Then dry, distilled and degassed toluene (15 ml) was added. The mixture was heated at 110°C during 24 hours. The original purple colour of the reaction turned to dark green. Ethyl acetate was added, and then the mixture was filtered on celite and evaporated. The resulted crude product was purified by flash column chromatography using an 85 to 15 mixture of petrol ether and DCM as eluent (R_f = 0.17) to obtain the title compound as a pure product (1.86 g, *90 %* yield).



Molecular formula: $C_{20}H_{18}O$

Molecular weight: 274.36 g/mol

Physical aspect: colourless oil

^{1}H-NMR (500 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.92	s	-	3	19
3.54	s	-	3	20
6.63	d	8.2	1	6
6.72	d	7.6	1	4
7.08-7.17	m	-	6	9, 10, 15, 16, 17, 18
7.20-7.25	m	-	1	5
7.37-7.46	m	-	3	8, 11, 14

^{13}C-NMR (125 MHz, $CDCl_3$)	
δ (ppm)	N°
20.28	19
55.37	20
107.81	6
122.09	4
127.34	14, 18
128.64	15, 17
126.36, 127.05, 127.38, 127.85, 129.66, 130.82	5, 8, 9, 10, 11, 16
130.17	2
136.03, 137.54, 141.75, 141.83	3, 7, 12, 13
156.92	1

Infrared spectrum (film, cm^{-1}): 3057w, 3018w, 2950w, 2933w, 2833w (C-H); 1597w, 1579m (aromatic C-C); 1467s; 1434w; 1296w; 1255s, 1083s (C-O); 995w; 910w; 777w; 761w; 744s; 700s.

Mass spectrum (APCI) m/z (relative intensity): 275 $[M+H]^+$ (100%), 260 (M-14, $[C_{19}H_{16}O]^{\cdot+}$) (35%); 243 (M-31, $[C_{19}H_{15}]^+$) (17%), 228 (M-46, $[C_{18}H_{12}]^{\cdot+}$) (6%).

High resolution mass spectrum (EI+, $M^{\cdot+}$): for $C_{20}H_{18}O$, calculated: 274.1358, found: 274.1361.

Separation of the enantiomers:

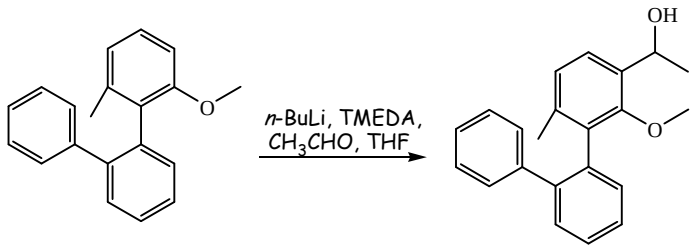
1. (at UCL) MPLC, semi-preparative chiral OD-H column (20µm); 99.7 to 0.3 mixture of hexane and isopropanol as eluent; 60 ml per minute rate of solvent; 40 mg product per injection.

2. (at UCB) HPLC, preparative chiral OD column (8*500mm); 99.8 to 0.2 mixture of benzene and isopropanol as eluent; 100 ml per minute rate of solvent; 320 mg product per injection.

$[\alpha]^{D}_{22}$: -134.2 (0.069 M, DCM) for the first fraction.

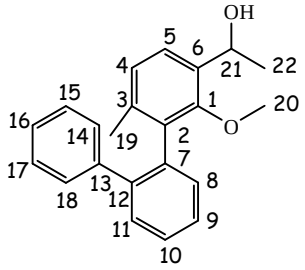
$[\alpha]^{D}_{23}$: +136.6 (0.045 M, DCM) for the second fraction.

IX. 4. 55. Preparation of 1-(2-methoxy-4-methyl-3-(2-phenyl-phenyl) phenyl)ethanol



The substrate (1.62 g, 5.9 mmol, 1 eq.) was dissolved in dry, freshly distilled diethyl ether (60 ml) under argon. Then TMEDA (1.8 ml, 11.9 mmol 2 eq.) was added followed by the dropwise addition of *n*-BuLi (7.4 ml, 1.6 M in hexane, 11.8 mmol, 2 eq.). After 2 hours stirring at room temperature, the mixture was cooled down to 0°C and acetaldehyde (1 ml, 17.7 mmol, 3 eq.) was added dropwise. The reaction was let warm up to room temperature. 3 hours later, it was quenched by the addition water, extracted with DCM, dried over $MgSO_4$, filtered and evaporated. The resulted crude product was

purified by flash column chromatography using DCM as eluent to obtain the title compound as a pure product (870 mg, *46%* yield). The diastereomers could be separated by flash column chromatography using a 6 to 1 mixture of petrol ether and ethyl acetate as eluent (R_f = 0.23 and 0.19).



Molecular formula: $C_{22}H_{22}O_2$

Molecular weight: 318.41 g/mol

Physical aspect: slightly yellow oil (A), white solid (B)

Diastereomer A:

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.43	d	6.5	3	22
1.99	s	-	3	19
2.15	d	3.5	1	OH
3.35	s	-	3	20
4.98	dq	6.4, 3.4	1	21
6.92	d	7.9	1	4
7.05-7.20	m	-	6	5, 9, 10, 15, 17, 18
7.29-7.36	m	-	1	16
7.36-7.52	m	-	3	8, 11, 14

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
20.32	19
22.49	22
60.75	20
65.30	21
127.50	14, 18
128.63	15, 17
125.05, 125.53, 126.52, 126.84, 127.77, 130.08, 131.04	4, 5, 8, 9, 10, 11, 16
134.63, 135.19, 135.58, 137.38, 141.46, 141.81	2, 3, 6, 7, 12, 13
155.16	1

Infrared spectrum (film, cm^{-1}): 3363bs (OH); 3057w, 3018w, 2968m, 2923m, 2860w (C-H); 1596w, 1577w (aromatic C-C); 1448s; 1402m; 1336w; 1250m; 1232m; 1126w; 1105w; 1068s (C-O); 1051w; 1036m, 1008m; 997w; 925w; 902m, 821s; 764m; 746s; 698s.

Mass spectrum (CI) m/z (relative intensity): 301 (M-17, $[C_{22}H_{21}O]^+$) (37%); 135 (M-183, $[C_9H_{11}O]^+$) (100%).

High resolution mass spectrum (ES+, M+Na): for $C_{22}H_{22}O_2Na$, calculated: 341.1517, found: 341.1515.

Diastereomer B:

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.25	d	6.4	3	22
1.98	s	-	3	19
2.19	s	-	1	OH
3.34	s	-	3	20
4.97	q	6.3	1	21
6.91	d	7.9	1	4
7.02-7.15	m	-	5	9, 10, 15, 17, 18
7.21	d	7.9	1	5
7.28-7.35	m	-	1	16
7.35-7.52	m	-	3	8, 11, 14

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
20.26	19
24.36	22
60.70	20
65.94	21
127.37	14, 18
128.60	15, 17
124.75, 125.50, 126.40, 126.78, 127.67, 129.99, 130.92	4, 5, 6, 9, 10, 11, 16
134.56, 135.69, 135.71, 136.96, 141.43, 141.82	2, 3, 7, 8, 12, 13
154.51	1

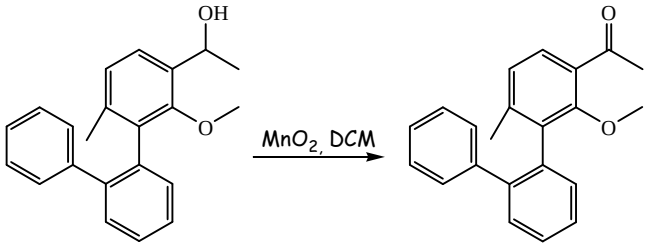
Infrared spectrum (film, cm^{-1}): 3400w (OH); 3057w, 3020w, 2970m, 2927m, 2864w (C-H); 1598w, 1578w (aromatic C-C); 1448s; 1402m; 1334w; 1251m; 1232m; 1126w; 1107w; 1072s (C-O); 1056w; 1037m, 997w; 925w; 902w, 821s; 764m; 744s; 700s.

Mass spectrum (CI) m/z (relative intensity): 319 $[M+H]^+$ (77%), 301 (M-17, $[C_{22}H_{21}O]^+$) (100%).

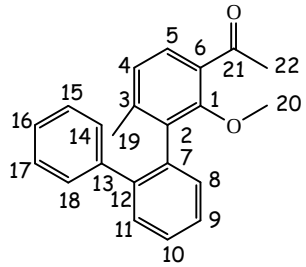
Melting point: 111-114°C

High resolution mass spectrum (ES+, M+Na): for $C_{22}H_{22}O_2Na$, calculated: 341.1517, found: 341.1522.

IX. 4. 56. Preparation of 1-(2-methoxy-4-methyl-3-(2-phenyl-phenyl) phenyl)ethanone



The alcohol (160 mg, 0.5 mmol, 1 eq.) was dissolved in DCM (10 ml) in a one-necked flask (50 ml). MnO_2 (1.5 g, 17.3 mmol, 34.5 eq.) was added to the solution and it was stirred at room temperature during 4 hours, when the conversion was complete. The reaction mixture was filtered through a short pad of celite and the collected organic layer was evaporated to obtain the title compound as a pure product (141 mg, *89%* yield).



Molecular formula: $C_{22}H_{20}O_2$

Molecular weight: 316.39 g/mol

Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.99	s	-	3	19
2.45	s	-	3	22
3.38	s	-	3	20
6.93	d	8.0	1	4
7.15	s	-	5	9, 10, 15, 17, 18
7.26-7.31	m	-	1	16
7.35-7.53	m	-	4	5, 8, 11, 14

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
20.72	19
30.35	22
61.77	20
125.36	4
127.56	14, 18
128.67	15, 17
126.63, 126.98, 127.94, 128.61, 130.09, 130.66*	5, 6, 8, 9, 10, 11, 16
134.99, 135.66	2, 3
141.24, 141.74, 142.80	7, 12, 13
157.21	1
200.76	21

*The peak at 130.66 probably contains the 6th quaternary carbon as well.

Infrared spectrum (film, cm^{-1}): 3057w, 3020w, 2966w, 2922w, 2850w (C-H); 1679s (C=O); 1593m, 1560w (aromatic C-C); 1456m; 1392m; 1355m; 1296s; 1234w; 1132w; 1051s (C-O); 1033w; 1001w; 966w; 923w; 821w; 764m; 746m; 702s.

Mass spectrum (APCI) m/z (relative intensity): 317 $[M+H]^+$ (27%), 299 (M-17, $[C_{22}H_{19}O]^+$) (34%); 287 (M-29, $[C_{21}H_{19}O]^+$) (100%), 260 (M-56, $[C_{19}H_{16}O]^{\cdot +}$) (42%), 243 (M-73, $[C_{19}H_{15}]^+$) (25%), 228 (M-88, $[C_{18}H_{12}]^{\cdot +}$) (20%) .

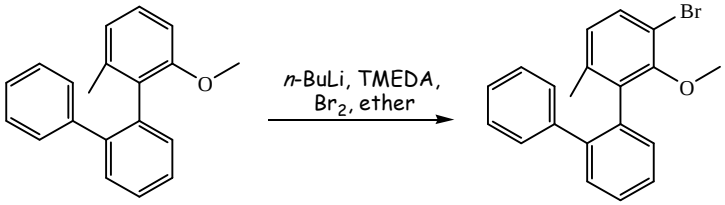
Melting point: 106-110°C

High resolution mass spectrum (ES+, M+Na): for $C_{22}H_{20}O_2Na$, calculated: 339.1361, found: 339.1365.

$[\alpha]^D_{20}$: +125.9 (0.032 M, DCM).

IX. 4. 57. Preparation of 2,6-bis(2-methoxy-4-methyl-3-(2-phenyl-phenyl)phenyl)pyridine

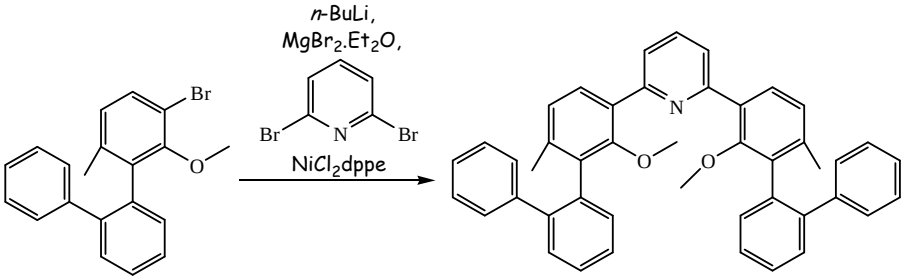
First step:



The substrate (2.43 g, 8.9 mmol, 1 eq.) was dissolved in dry, freshly distilled diethyl ether (88 ml) under argon. Then TMEDA (2.7 ml, 17.9 mmol 2 eq.) was added followed by the dropwise addition of *n*-BuLi (11 ml, 1.6 M in hexane, 17.6 mmol, 2 eq.). After 2 hours stirring at room temperature, the mixture was cooled down to -78°C and bromine (20 ml, 0.9 M in hexane, 18 mmol, 2 eq.) was added dropwise. The reaction was let warm up to room temperature. 3 hours later, it was quenched by the addition of 10 % $Na_2S_2O_3$ aqueous solution, extracted with DCM, dried over $MgSO_4$, filtered and evaporated. The ^{1}H-NMR showed around *60%* conversion. The resulted crude product was purified by flash column chromatography using an 85 to 15 mixture of petrol ether and DCM as eluent (R_f =

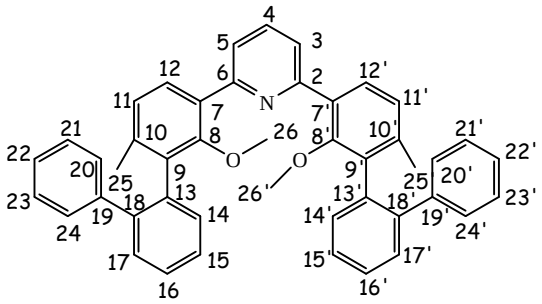
0.15) to obtain a pure mixture of starting material and brominated product (2.46 g, *35%* starting material and *65%* brominated product). We used this purified mixture as starting material in the next step of the synthesis.

Second step:



A portion of the previous mixture (500 mg, *65 %* brominated product, 1 mmol, 1 eq.) was placed in a dry, two-necked flask (25 ml), under argon. Dry, freshly distilled diethyl ether (3 ml) was added and the solution was treated with *n*-BuLi (0.75 ml, 1.6 M in hexane, 1.2 mmol, 1.2 eq.). By the addition it turned to yellow. After 30 min stirring at room temperature, a diethyl ether solution (5 ml) of $MgBr_2xEt_2O$ (284 mg, 1.1 mmol, 1.1 eq.) was added dropwise. The colour of the solution turned immediately to white. Meantime, 2,6-dibromopyridine (120 mg, 0.5 mmol, 0.5 eq.) and $NiCl_2$dppe (53 mg, 0.1 mmol, 0.1 eq.) were placed in a condenser-equipped, dry, two-necked flask (25 ml), under argon. Dry, freshly distilled THF (2.5 ml) was added and it was cooled down to 0°C. The previously prepared magnesium reagent was added dropwise. Then, the mixture was heated at 65-70°C overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution, extracted with DCM, dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using DCM as eluent

(R_f = 0.80) to obtain the title compound as a pure product (74 mg, *24%* yield).



Molecular formula:

$C_{45}H_{37}NO_2$

Molecular weight:

623.78 g/mol

Physical aspect:

white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.96	s	-	6	25, 25’
3.18	s	-	6	26, 26’
6.99	d	7.9	2	11, 11’
7.08-7.33	m	-	12	15, 15’, 16, 16’, 21, 21’, 22, 22’, 23, 23’, 24, 24’
7.36-7.53	m	-	6	14, 14’, 17, 17’, 20, 20’
7.53-7.65	m	-	3	3, 4, 5
7.68	d	7.9	2	12, 12’

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
20.43	25, 25’
60.78	26, 26’
122.36	3, 5
125.57, 126.50, 126.86, 127.56, 129.92, 130.29, 130.73	11, 11’, 12, 12’, 14, 14’, 15, 15’, 16, 16’, 17, 17’, 22, 22’
127.58	20, 20’, 24, 24’
128.85	21, 21’, 23, 23’
135.39, 136.02, 136.05, 138.48, 141.50, 141.52	4, 9, 9’, 10, 10’, 13, 13’, 18, 18’, 19, 19’
155.65	2, 6
156.03	8, 8’

7, 7’ overlap with one of the peaks.

Infrared spectrum (film, cm^{-1}): 3057w, 3020w, 2927w, 2854w (C-H); 1596m, 1573m (aromatic C-C); 1444s; 1365w; 1249w; 1051m (C-O); 910w, 804m; 744s; 700s.

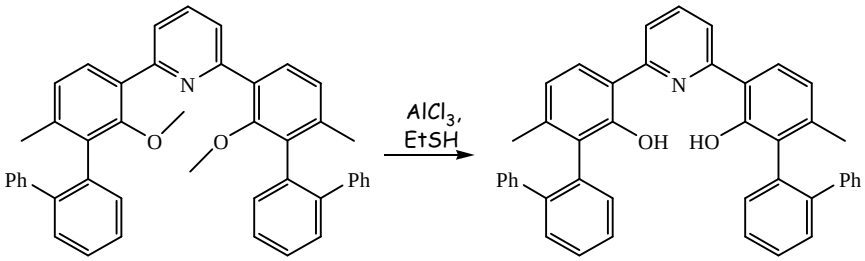
Mass spectrum (APCI) m/z (relative intensity): 624 $[M+H]^+$ (100%), 608 (M-15, $[C_{44}H_{34}NO_2]^+$) (20%), 594 (M-29, $[C_{43}H_{32}NO_2]^+$) (18%); 532 (M-91, $[C_{41}H_{26}N]^+$) (13%).

Melting point: 157-160°C

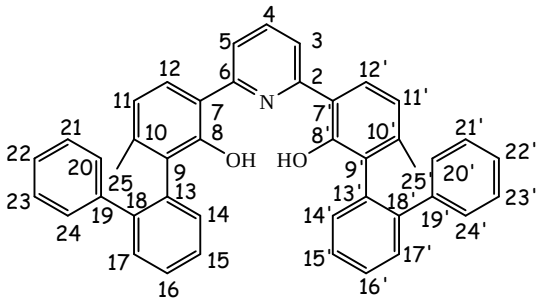
High resolution mass spectrum (ES+, $M+H^+$): for $C_{45}H_{38}NO_2$, calculated: 624.2903, found: 624.2897.

$[\alpha]^D_{22}$: -258.6 (0.018 M, DCM).

IX. 4. 58. Preparation of pyridin-2,6-diyl-bis(4-methyl-3-(2-phenyl-phenyl)-2-phenol)



Anhydrous $AlCl_3$ (115 mg, 0.86 mmol, 3 eq./OMe) was placed in a two-necked flask (10 ml), under argon. EtSH (1.4 ml) was added and the mixture was cooled down to 0°C. The substrate (89 mg, 0.14 mmol, 1 eq.) was added to the mixture and it was let warm up to room temperature. An orange coloured clear solution was obtained. After overnight stirring, water was added, acidified to pH=1, extracted with DCM, dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 1 to 1 mixture of petrol ether and DCM as eluent (R_f = 0.41) to obtain the title compound as a pure product (53 mg, *62%* yield).



Molecular formula:

$C_{43}H_{33}NO_2$

Molecular weight:

595.73 g/mol

Physical aspect:

lemon yellow solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.85	s	-	6	25, 25’
6.68	d	8.1	2	11, 11’
7.04-7.14	m	-	6	15, 15’, 16, 16’, 22, 22’
7.18-7.26	m	-	4	21, 21’, 23, 23’
7.28-7.36	m	-	2	24, 24’
7.40-7.54	m	-	8	12, 12’, 14, 14’ 17, 17’ 20, 20’
7.65	d	8.0	2	3, 5
7.84	t	8.0	1	4
9.98	bs	-	2	OH

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
20.37	25, 25’
119.26	7, 7’
119.48	3, 5
121.19	11, 11’
126.66	22, 22’
127.05	12, 12’
127.54, 128.06	15, 15’, 16, 16’
127.72	20, 20’, 24, 24’
128.67	21, 21’, 23, 23’
129.88	9, 9’
130.29, 131.16	14, 14’, 17, 17’
135.01, 138.34, 141.28, 142.31	10, 10’, 13, 13’, 18, 18’, 19, 19’
139.60	4
154.05	8, 8’
155.93	2, 6

Infrared spectrum (film, cm^{-1}): 3523w (OH); 3055w, 3020w, 2920w, 2850w (C-H); 1612m, 1577m (aromatic C-C); 1465w; 1448w; 1433w; 1419w; 1409w; 1245m; 1172m (C-O); 908m; 794m; 742s; 700s.

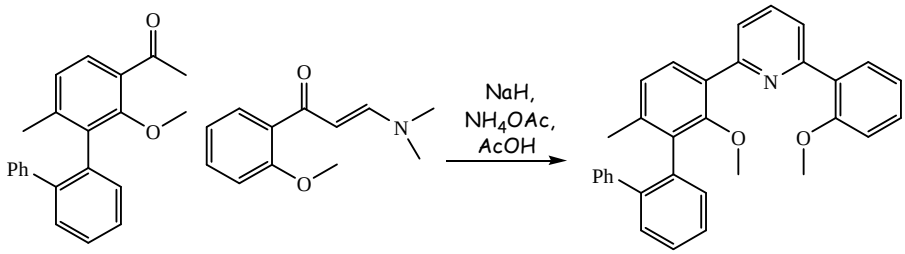
Mass spectrum (APCI) m/z (relative intensity): 596 $[M+H]^+$ (100%).

Melting point: 98-100°C

High resolution mass spectrum (ES+, M+Na): for $C_{43}H_{33}NO_2Na$, calculated: 618.2409, found: 618.2430.

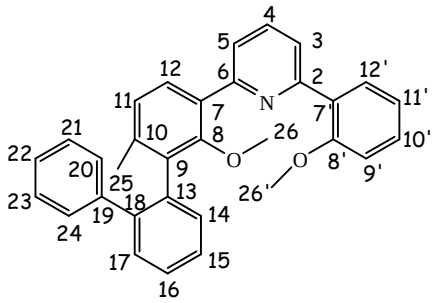
$[\alpha]^D_{22}$: - 538.7 (0.016 M, DCM).

IX. 4. 59. Preparation of 2-(2-methoxy-4-methyl-3-(2-phenyl-phenyl) phenyl)-6-(2-methoxyphenyl)pyridine



NaH (185 mg, 60 w/w%, 4.63 mmol, 2 eq.) was suspended in dry, distilled THF (10 ml) in a two-necked flask (100 ml) under argon. The ketone (722 mg, 2.28 mmol, 1 eq.) dissolved in THF (4 ml) was added to the suspension dropwise. During this addition there was nearly no bubbling. After 15 minutes stirring at room temperature, the enaminone (936 mg, 4.56 mmol, 2 eq.) dissolved in THF (4 ml) was added dropwise. Intensive bubbling was observed during this addition. The orange mixture was stirred at room temperature overnight. After a few hours, some precipitation appeared in the solution. Then, glacial acetic acid (11.5 ml, 5 ml/mmol ketone) was added followed by

ammonium acetate (1.76 g, 22.83 mmol, 10 eq.). The mixture was refluxed at 110°C during 2 hours. Then it was let cool down to room temperature, concentrated on the vacuum pump and re-dissolved in DCM. It was washed with saturated aqueous solution of $NaHCO_3$, dried over Na_2SO_4, filtered and evaporated. The resulted crude product was purified by column chromatography using a 20 to 1 mixture of toluene and ethyl acetate as eluent (R_f = 0.63) to obtain the title compound as a pure product (796 mg, *76%* yield).



Molecular formula: $C_{32}H_{27}NO_2$

Molecular weight: 457.56 g/mol

Physical aspect: white solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.95	s	-	3	25
3.20	s	-	3	26
3.86	s	-	3	26’
6.99	m	-	2	9’, 11
7.04-7.54	m	-	11	10’, 11’, 14, 15, 16, 17, 20, 21, 22, 23, 24
7.56-7.80	m	-	4	3, 4, 5, 12
7.95	dd	7.6, 1.7	1	12’

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
20.42	25
55.58	26’
60.93	26
111.41	9’
121.03	5
122.41	3
122.95	11’
125.27	9
125.53, 126.50, 126.85, 127.53, 129.75, 130.41, 130.76	11, 12, 14, 15, 16, 17, 22
128.19, 129.00	7, 7’
127.57	20, 24
128.87	21, 23
129.91	10’
131.38	12’
135.33, 135.64, 136.14	13, 18, 19
138.36	4
141.56	10
155.27	6
155.71	8
155.96	2
157.11	8’

Infrared spectrum (film, cm^{-1}): 3057w, 3020w, 2931w, 2835w (C-H); 1598m, 1581m, 1568m (aromatic C-C); 1490m; 1444s; 1375w; 1257s; 1238m; 1053m; 1026m; 810m; 754s; 746s; 700m.

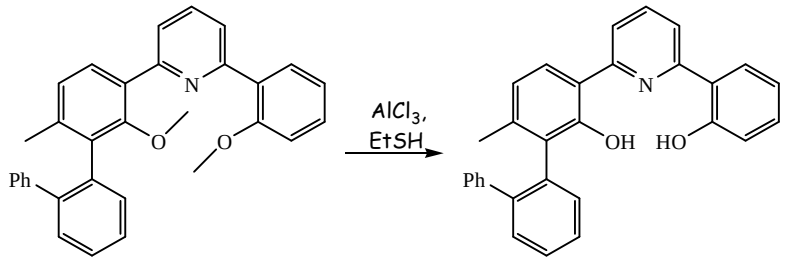
Mass spectrum (APCI) m/z (relative intensity): 457 $[M]^{\cdot +}$ (100%).

Melting point: 50-53°C

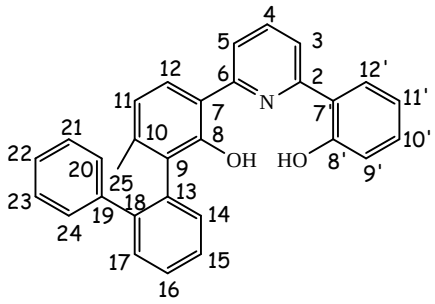
High resolution mass spectrum (ES+, M+Na): for $C_{32}H_{27}NO_2Na$, calculated: 480.1939, found: 480.1932.

$[\alpha]^{D}_{21}$: +197.6 (0.023 M, DCM).

IX. 4. 60. Preparation of 2-(6-(2-hydroxy-4-methyl-3-(2-phenyl-phenyl)phenyl)pyridin-2-yl)phenol



Anhydrous $AlCl_3$ (477 mg, 3.58 mmol, 3 eq./OMe) was placed in a two-necked flask (25 ml), under argon. EtSH (6 ml) was added and the mixture was cooled down to 0°C. The substrate (273 mg, 0.60 mmol, 1 eq.) was added to the mixture and it was let warm up to room temperature. An orange coloured clear solution was obtained. After overnight stirring, water was added, acidified to pH=1, extracted with DCM, dried over $MgSO_4$, filtered and evaporated. The resulted crude product was purified by flash column chromatography using a 1 to 1 mixture of petrol ether and DCM as eluent (R_f = 0.16) to obtain the title compound as a pure product (179 mg, *70%* yield).



Molecular formula: $C_{30}H_{23}NO_2$

Molecular weight: 429.51 g/mol

Physical aspect: lemon yellow solid

^{1}H-NMR (300 MHz, $CDCl_3$)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.86	s	-	3	25
6.73	d	8.0	1	11
6.93	t	7.6	1	11’
6.99	d	8.2	1	9’
7.10-7.36	m	-	7	10’, 15, 16, 20, 21, 23, 24
7.40-7.56	m	-	4	12, 14, 17, 22
7.66	dd	7.9, 1.7	3	3, 5, 12’
7.88	t	8.0	1	4
10.15	bs	-	2	OH

^{13}C-NMR (75 MHz, $CDCl_3$)	
δ (ppm)	N°
20.35	25
117.99	9’
118.71, 119.57, 120.41	3, 5, 11’
119.76, 121.06	7, 7’
121.55	11
126.77, 127.50, 127.58, 127.75, 128.30, 130.44, 130.95, 131.27	10’, 12, 12’, 14, 15, 16, 17, 22
127.75	20, 24
128.63	21, 23
129.75	9
134.43	13
138.83	4
139.71, 141.08	18, 19
142.36	10
153.14	8
155.60, 156.28	2, 6
157.36	8’

Infrared spectrum (film, cm^{-1}): 3340bs (OH); 3057w, 2921w (C-H); 1610m, 1593s, 1562m (aromatic C-C); 1456s; 1429s; 1398w; 1375w; 1286m; 1257s; 1245m; 1176s (C-O); 908s; 800m; 754s; 732s; 700s.

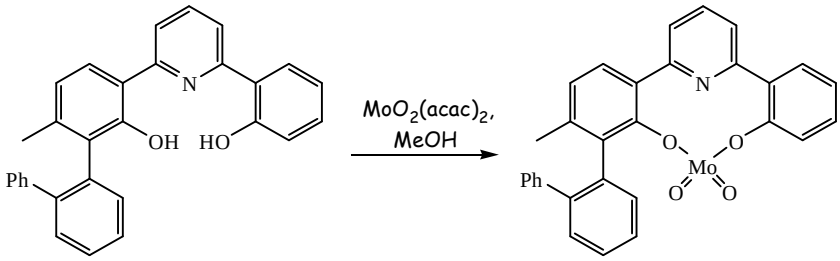
Mass spectrum (ESI) m/z (relative intensity): 430 $[M+H]^+$ (100%).

Melting point: 89-91°C

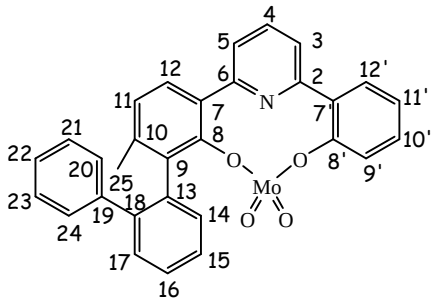
High resolution mass spectrum (ES+, $M+H^+$): for $C_{30}H_{24}NO_2$, calculated: 430.1807, found: 430.1792.

$[\alpha]^{D}_{21}$: +456.5 (0.024 M, DCM).

IX. 4. 61. Preparation of dioxomolybdenum (pyridin-2-yl-(4-methyl-3-(2-phenyl-phenyl)-2-phenolate)-6-yl-(2-phenolate))



$MoO_2(acac)_2$ (38 mg, 0.12 mmol, 1 eq.) was dissolved in MeOH (1.0 ml). The ligand (50 mg, 0.12 mmol, 1 eq.) was added to the solution and it was stirred at room temperature during a few hours. The mixture was concentrated, and then, diethyl ether (3 x 1 ml) and methanol (3 x 1 ml) was evaporated from the crude to obtain complete conversion.



Molecular formula: $C_{30}H_{21}MoNO_4$

Molecular weight: 555.43 g/mol

Physical aspect: lemon yellow solid

^{1}H-NMR (500 MHz, CD_3OD)				
δ (ppm)	Mult.	J (Hz)	Int.	N°
1.74	s	-	3	25
6.69	d	8.2	1	11
6.96-7.03	m	-	2	9', 11'
7.05-7.10	m	-	3	10', 15, 16
7.21-7.26	m	-	2	21, 23
7.34-7.47	m	-	4	17, 20, 22, 24
7.50	d	7.3	1	14
7.65	d	8.2	1	12
7.82	d	8.0	1	12'
7.99	d	7.9	1	3
8.01	d	8.1	1	5
8.07	t	7.9	1	4

^{13}C-NMR (125MHz, CD_3OD)	
δ (ppm)	N°
20.42	25
119.78	9'
121.74, 123.34, 123.87, 124.14	3, 5, 11, 11'
125.22	7
127.61	7'
127.53, 128.27, 128.55, 128.96, 130.36, 130.74	10', 14, 15, 16, 17, 22
128.64	20, 24
130.12	21, 23
131.61	9
132.21, 132.46	12, 12'
137.30, 141.09, 143.06, 143.15	10, 13, 18, 19
140.72	4
155.54, 156.05	2, 6
162.92, 163. 21	8, 8'

Infrared spectrum (film, cm^{-1}): 2916w, 2849w (C-H); 1595m, 1578m (aromatic C-C); 1443m; 1433w; 1411w; 1367w; 1285m; 1253m; 1190w; 1124w; 1034w; 941s, 914s (Mo=O); 840w; 804w; 760s.

Mass spectrum (APCI) m/z (relative intensity): 558 $[M+H]^+$ (30%); 430 (M-127, $[C_{30}H_{24}NO_2]^+$) (100%).

Melting point: 145-150°C

High resolution mass spectrum (ES+, $M+H^+$): for $C_{30}H_{22}NO_4Mo$, calculated: 558.0603, found: 558.0618. (The highest molecular peak, corresponding to Mo^{98}, the most abundant molybdenum isotope, was chosen for the interpretation.)

$[\alpha]^D_{20}$: +401.8 (0.027 M, MeOH).

IX. 4. 62. General oxidation procedure

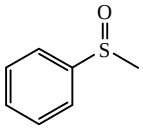
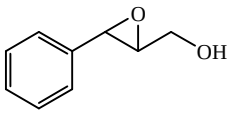
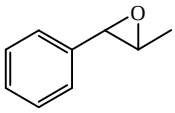
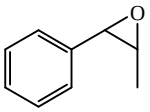
Internal standard (usually dodecane) and catalyst was added to a 0.5 M solution of the substrate. After mixing, a few µl of starting sample was taken. Then, the temperature was set and the required equivalent *t*-BuOOH (5.5 M in decane) was added dropwise. The conversion was usually followed by gas chromatography. For that, the aliquots were highly diluted, washed with water and dried over $MgSO_4$. Identification of the peaks were carried out by co-injections with standard compounds.

IX. 4. 63. Determination of enantiomeric excess

Racemic mixtures of the required products were prepared by standard procedures using mCPBA as oxidizing agent. These mixtures

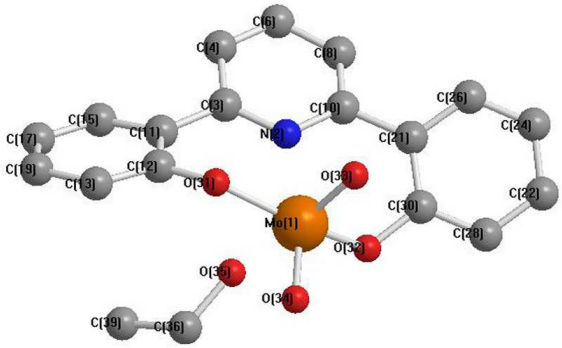
were used to find the ideal methods and conditions for the separation of enantiomers.

Applied methods and conditions:

Substrates	Methods and conditions
	HPLC on chiral OD-H column Hexane : *i*-PrOH = 85 : 15 1ml/min t_1 = 10.25 min; t_2 = 11.60 min
	HPLC on chiral OD-H column Hexane : *i*-PrOH = 95 : 5 1ml/min t_1 = 19.77 min; t_2 = 22.35 min
	GC on chiral GTA column 80°C for 2 min, then + 4°C/min to 135°C t_1 = 8.52 min; t_2 = 9.45 min
	GC on chiral CP-Chirasil-Dex CB column 90°C for 16 min, then + 10°C/min to 140°C t_1 = 17.83 min; t_2 = 18.66 min

IX. 5. X-ray analyses

IX. 5. 1. Dioxomolybdenum (pyridin-2,6-diyl-bis(2-phenolate))



Empirical formula: $C_{17}H_{13}MoNO_5$
Space group: P-1
Cell lengths: a: 8.628 Å; b: 9.797 Å; c: 13.215 Å
Cell angles: α: 106.32; β: 106.34; γ: 91.33
Cell volume: 1022.37 $Å^3$
Z: 2
R_1: 0.044 (4217 obs.)

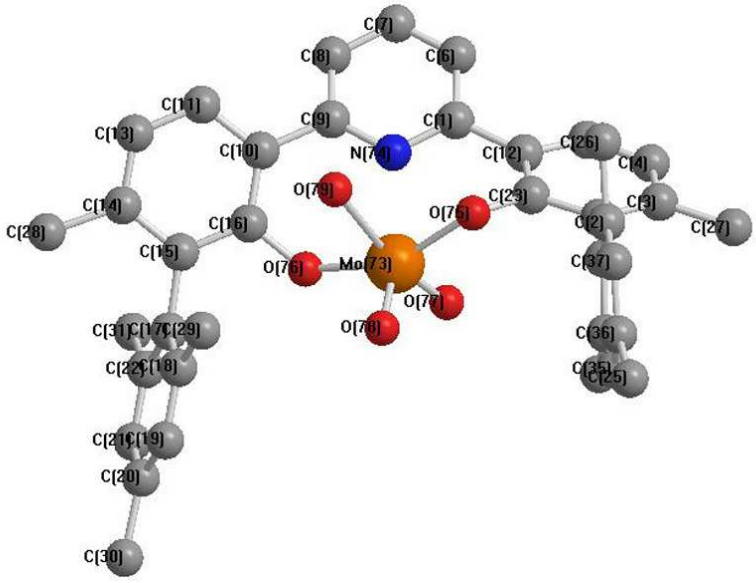
Selected bond lengths:

Bonds	*Bond lengths (Å)*	*Bonds*	*Bond lengths (Å)*
Mo(1)-O(31)	1.94	N(2)-C(10)	1.37
Mo(1)-O(32)	1.97	C(3)-C(11)	1.48
Mo(1)-O(33)	1.70	C(10)-C(21)	1.49
Mo(1)-O(34)	1.69	C(11)-C(12)	1.39
Mo(1), O(35)	2.29	C(21)-C(30)	1.40
Mo(1), N(2)	2.39	C(12)-O(31)	1.34
N(2)-C(3)	1.36	C(30)-O(32)	1.36

Selected bond angles:

Bonds	*Bond angles (degree)*	*Bonds*	*Bond angles (degree)*
O(31)-Mo(1)-O(32)	153.14	O(34)-Mo(1), O(35)	86.27
O(31)-Mo(1)-O(33)	97.91	O(34)-Mo(1), N(2)	163.49
O(31)-Mo(1)-O(34)	99.58	C(3)-N(2)-C(10)	118.26
O(31)-Mo(1), O(35)	83.41	N(2)-C(3)-C(11)	121.52
O(31)-Mo(1), N(2)	78.63	C(3)-C(11)-C(12)	122.96
O(32)-Mo(1)-O(33)	95.54	C(11)-C(12)-O(31)	121.49
O(32)-Mo(1)-O(34)	99.26	C(12)-O(31)-Mo(1)	131.13
O(32)-Mo(1), O(35)	78.88	Mo(1)-O(32)-C(30)	120.51
O(32)-Mo(1), N(2)	77.86	O(32)-C(30)-C(21)	121.29
O(33)-Mo(1)-O(34)	104.95	C(30)-C(21)-C(10)	122.63
O(33)-Mo(1), O(35)	168.23	C(21)-C(10)-N(2)	120.62
O(33)-Mo(1), N(2)	91.53		

IX. 5. 2. Dioxomolybdenum (pyridin-2,6-diyl-bis(4-methyl-3-(2,4,6-trimethylphenyl)-2-phenolate))



Empirical formula: $C_{37}H_{35}MoNO_5$

Space group: P-1

Cell lengths: a: 10.722 Å; b: 11.305 Å; c: 15.467 Å

Cell angles: α: 102.890; β: 96.350; γ: 94.940

Cell volume: 1804.42 $Å^3$

Z: 2

R_1: 0.067 (2713 obs.)

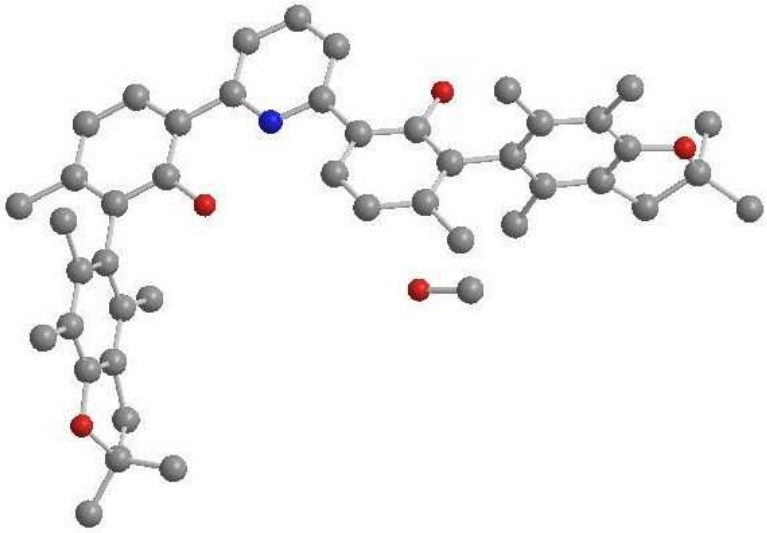
Selected bond lengths:

Bonds	*Bond lengths (Å)*	*Bonds*	*Bond lengths (Å)*
Mo(73)-O(76)	1.93	N(74)-C(1)	1.35
Mo(73)-O(75)	1.95	C(9)-C(10)	1.49
Mo(73)-O(77)	1.71	C(1)-C(12)	1.48
Mo(73)-O(78)	1.69	C(10)-C(16)	1.39
Mo(73), O(79)	2.34	C(12)-C(23)	1.42
Mo(73), N(74)	2.33	C(16)-O(76)	1.36
N(74)-C(9)	1.36	C(23)-O(75)	1.34

Selected bond angles:

Bonds	*Bond angles (degree)*	*Bonds*	*Bond angles (degree)*
O(76)-Mo(73)-O(75)	154.16	O(78)-Mo(73), O(79)	84.77
O(76)-Mo(73)-O(77)	97.64	O(78)-Mo(73), N(74)	160.80
O(76)-Mo(73)-O(78)	99.53	C(1)-N(74)-C(9)	118.07
O(76)-Mo(73), O(79)	85.39	N(74)-C(9)-C(10)	121.14
O(76)-Mo(73), N(74)	79.35	C(9)-C(10)-C(16)	123.44
O(75)-Mo(73)-O(77)	95.89	C(10)-C(16)-O(76)	119.63
O(75)-Mo(73)-O(78)	97.95	C(16)-O(76)-Mo(73)	130.34
O(75)-Mo(73), O(79)	77.40	Mo(73)-O(75)-C(23)	119.39
O(75)-Mo(73), N(74)	77.89	O(75)-C(23)-C(12)	119.86
O(77)-Mo(73)-O(78)	105.38	C(23)-C(12)-C(1)	121.47
O(77)-Mo(73), O(79)	168.67	C(12)-C(1)-N(74)	120.72
O(77)-Mo(73), N(74)	93.74		

IX. 5. 3. 2,6-bis(3-(2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-5-yl)-2-hydroxy-4-methylphenyl)pyridine



Empirical formula: $C_{47}H_{49}NO_6$

Space group: $P2_1$

Cell lengths: a: 10.513 Å; b: 14.257 Å; c: 14.692 Å

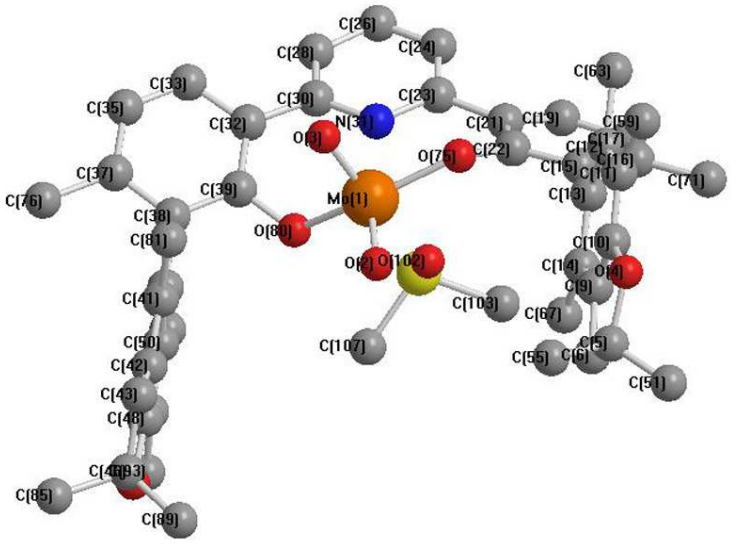
Cell angles: α: 90.00; β: 108.42; γ: 90.00

Cell volume: 2089.27 $Å^3$

Z: 2

R_1: 0.056 (8030 obs.)

IX. 5. 4. Dioxomolybdenum (pyridin-2,6-diyl-bis((2,3-dihydro-2,2,4, 6,7-pentamethylbenzofuran-5-yl)-6-methyl-2-phenol-ate))



Empirical formula: $C_{48}H_{57}MoNO_8S$

Space group: $P2_12_12_1$

Cell lengths: a: 8.411 Å; b: 18.980 Å; c: 28.612 Å

Cell angles: α: 90.00; β: 90.00; γ: 90.00

Cell volume: 4567.64 $Å^3$

Z: 4

R_1: 0.073 (3652 obs.)

Absolut structure parameter: -0.01 (9)

Selected bond lengths:

Bonds	*Bond lengths (Å)*	*Bonds*	*Bond lengths (Å)*
Mo(1)-O(75)	1.93	N(31)-C(30)	1.37
Mo(1)-O(80)	1.94	C(23)-C(21)	1.51
Mo(1)-O(2)	1.67	C(30)-C(32)	1.48
Mo(1)-O(3)	1.71	C(21)-C(22)	1.41
Mo(1), O(102)	2.21	C(32)-C(39)	1.41
Mo(1), N(31)	2.40	C(22)-O(75)	1.33
N(31)-C(23)	1.39	C(39)-O(80)	1.36

Selected bond angles:

Bonds	*Bond angles (degree)*	*Bonds*	*Bond angles (degree)*
O(75)-Mo(1)-O(80)	153.23	O(3)-Mo(1), O(102)	166.80
O(75)-Mo(1)-O(2)	99.55	O(3)-Mo(1), N(31)	88.73
O(75)-Mo(1)-O(3)	96.06	C(30)-N(31)-C(23)	117.93
O(75)-Mo(1), O(102)	82.87	N(31)-C(23)-C(21)	118.85
O(75)-Mo(1), N(31)	78.60	C(23)-C(21)-C(22)	122.86
O(80)-Mo(1)-O(2)	100.59	C(21)-C(22)-O(75)	122.72
O(80)-Mo(1)-O(3)	95.76	C(22)-O(75)-Mo(1)	130.82
O(80)-Mo(1), O(102)	80.19	Mo(1)-O(80)-C(39)	121.53
O(80)-Mo(1), N(31)	77.74	O(80)-C(39)-C(32)	121.01
O(2)-Mo(1)-O(3)	104.53	C(39)-C(32)-C(30)	122.02
O(2)-Mo(1), O(102)	88.60	C(32)-C(30)-N(31)	121.95
O(2)-Mo(1), N(31)	166.74		