Åbo Akademi University

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To my family

PREFACE

This work was carried out at the Laboratory of Organic Chemistry, Åbo Akademi University during the period of Feb 2009 – May 2016. *The Academy of Finland*, *the Magnus Ehrnrooth Foundation* and *Rector of Åbo Akademi University* are gratefully acknowledged for the financial support.

I wish to express my deep gratitude to my supervisor Docent Patrik Eklund for giving me the opportunity to explore the field of chemistry of natural compounds. I am truly thankful for his endless support and for the inspiring discussions & ideas.

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I am very thankful to my co-authors Thomas Sandberg, Matti Hotokka, Rainer Sjöholm and Mikko Hänninen for productive research cooperation. I wish to thank Reko Leino, Jari Sinkkonen, Leif Kronberg for their help and scientific expertise. Many thanks to my friend and college Denys Mavrynsky for productive discussions, sharing his experience and good advices. Special thanks to Päivi Pennanen for her valuable help of resolving different kind of problems. Annika Smeds, Markku Reunanen, Axel Meierjohann and Matilda Kråkström are sincerely thanked for help with HPLC and mass spectra measurements.

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Big thanks to other Åbo Akademi colleges and to all good people who surrounded me during these years and helped me to adapt in Finland. Thank you, Ekaterina Korotkova, Anton Tokarev, Alexey Kirilin, Zhanna Boeva, Viktor Lukashov, Maria Plativa, Vadim Koveshnikov, Anastasia Kovershnikova, Maxim Skaldin, Oksana Skaldina etc.

I am grateful for my father Alexander and my mother Valentina who always cared, respected my choices and supported all my decisions even though they did not like some of them.

Thanks to my wife Anna, your love and care, giving me motivation and energy to get better and grow personally & professionally. Last but not least, thanks to my son Mihail, who is making my life brighter every day!

Yury Brusentsev

Åbo, January 2017

ABSTRACT

Finland has a long history of utilizing wood as fuel, construction material and for paper production. However, modern reality raises the question of more efficient and advanced utilization of wood-based natural products. One promising family of compounds are lignans, which are highly abundant in wood knots, especially hydroxymatairesinol (HMR). Having a complex structure and few chirally pure stereocenters, HMR could be used for preparation of valuable fine chemicals. One of the most efficient ways to utilize the complex chiral structure would be as ligands in asymmetric catalysis. Herein the development of asymmetric catalysts based on the structure of HMR is described.

In the first part of the thesis, the concept of using hydroxymatairesinol as a starting material for creating asymmetric catalysts as well as molecular modeling to confirm the concept are presented.

The second part of this work describes the synthetic modification of hydroxymatairesinol towards chiral diols. A series of chiral diols were prepared and examined as ligands in asymmetric catalytic reactions.

Parts 3 and 4 are related to the preparation of phosphorous derivatives. Part 3 is concentrated on H-phosphonates and phosphates prepared from the chiral diols described in the second part. In part 4, the synthesis of chiral phosphines based on the lignan backbone is described. The applications of the phosphines as ligands in rhodium catalyzed asymmetric hydrogenations are disclosed.

SAMMANFATTNING

Finland har en lång historia av att använda trä som bränsle, byggmaterial och för produktion av papper. I dagen samhälle finns en strävan mot ytterligare en mera effektiv och avancerad användning av träbaserade produkter. En lovande familj av föreningar som kunde utnyttjas i avancerade tillämpningar är lignaner. Lignaner förekommer rikligt i de inre kvistarna (kvistnötter) hos barrväxter, särskilt hydroximatairesinol (HMR) förekommer riktigt i gran. Hydroximatairesinol har en komplex struktur och några kiralt rena stereocentra varför dess struktur potentiellt kunde användas för framställning av värdefulla finkemikalier. Ett alternativ att effektivt kunna utnyttja den komplexa kirala strukturen skulle vara att använda strukturen som ligander i asymmetrisk katalys. Denna avhandling beskriver utvecklingen av asymmetriska katalysatorer baserade på strukturen hos hydroximatairesinol.

I den första delen av avhandlingen presenteras konceptet att använda hydroximatairesinol som utgångsmaterial för att skapa asymmetriska katalysatorer. Denna diskussion stöds av molekylmodellering och konformationsanalys.

Den andra delen av avhandlingen beskriver syntetisk modifiering av hydroximatairesinol till kirala dioler. En serie av kirala dioler framställdes och deras användning som ligander i asymmetriska katalytiska reaktioner undersöktes.

Del 3 och 4 är relaterade till framställning av fosforderivat av de tidigare framställda diolerna. Del 3 är koncentrerad på framställningen av fosfiter och fosfater och i del 4 beskrivs syntesen av kirala fosfiner. De framställda fosfinernas egenskaper som kirala ligander i rodium katalyserade asymmetriska hydrogeneringar beskrivs.

LIST OF PUBLICATIONS

This thesis is based on the following publications:

I Sandberg T, Brusentsev Y, Eklund P, Hotokka M. **Structural analysis of sterically hindered 1,4-diols from the naturally occurring lignan hydroxymatairesinol a quantum chemical study**. *Int. J. Quantum Chem.* **2011**; 111: 4309–4317

II Brusentsev Y, Sandberg T, Hotokka M, Sjöholm R, Eklund P. **Synthesis and structural analysis of sterically hindered chiral 1,4-diol ligands derived from the lignan hydroxymatairesinol***. Tetrahedron Lett.* **2013**; 54: 1112–1115

III Brusentsev Y, Hänninen M, Eklund P. **Synthesis of Sterically Hindered Chiral 1,4-Diols from Different Lignan-Based Backbones**. *Synlett* **2013**; 24: 2423–2426

IV Brusentsev Y, Eklund P. **Synthesis and applications of diphosphine ligands derived from the lignan hydroxymatairesinol.** *Catal. Today* **2015**; 241: 260–263

V Brusentsev Y, Eklund P. **Synthesis of chiral phosphorous and phosphoric acid derivatives from the lignans Matairesinol and Conidendrin.** *Synlett,* **2016**; 27: 2557-2560

CONTRIBUTION OF THE AUTHOR

This thesis is based on five original publications. The author of this thesis is the main author of papers II-V. In paper I, the quantum chemical investigation was performed in collaboration with Thomas Sandberg and Professor Matti Hotokka, Laboratory of Physical Chemistry, Åbo Akademi University. The author is fully responsible for the experimental work presented in publications **II**-**V** with the following exceptions:

- Performing the high resolution mass analyses
- Operating the X-ray diffractometer and processing the results
- Performing the DFT calculations presented in **I** and **II** publications

SELECTED CONFERENCE AND SEMINAR CONTRIBUTIONS

I Brusentsev, Yury; Eklund, Patrik, **Syntheses and applications of chirally pure phosphine ligands from the natural lignan hydroxymataresinol**,10th Congress on Catalysis Applied to Fine Chemicals, June 16-19, 2013, Åbo Akademi University, Åbo, Finland.

II Brusentsev, Yury; Eklund, Patrik, **Syntheses and applications of chirally pure phosphine ligands from the natural lignan hydroxymataresinol**, Summer School in Synthetic Organic Chemistry, June 2012, Åbo Akademi, Åbo, Finland.

III Brusentsev, Yury; Eklund, Patrik, **Syntheses and applications of chirally pure phosphine ligands from the natural lignan hydroxymataresinol**, 243rd ACS National Meeting&Exposition, San Diego, CA, United States, March 25-March 29, 2012, poster presentation.

IV Brusentsev, Yury; Eklund, Patrik, **Lignans as a new possible source of asymmetric organocatalysts**,1st ORCA Summit in Berlin March 2 - March 5, 2011, Humboldt-University Berlin, poster presentation

V Brusentsev, Yury; Eklund, Patrik, Rainer Sjöholm, **Lignans from paper industry waste as a new source of chiral 1,4-diols for asymmetric catalysts**, Summer School in Synthetic Organic Chemistry, Jyväskylä, Finland, August 16-17, 2010

VI Brusentsev, Yury; Eklund, Patrik, Rainer Sjöholm, **Lignans from paper industry waste as a new source of chiral 1,4-diols for asymmetric catalysts**,18th International Conference on Organic Synthesis, Bergen, Norway, August 1-August 6, 2010, poster presentation.

VII Brusentsev, Yury; **Lignan based sterically hindered 1,4-diols and their application for catalysis**, Summer school Seili, Finland, 17.-20.8.2009 , oral presentation.

VIII Brusentsev, Yury; Eklund, Patrik, Rainer Sjöholm, **Lignans from paper industry waste as a new source of chiral 1,4-diols for asymmetric catalysts**, COST Chemistry D40, Innovative Catalysis: New processes and selectivities, May 26-28, 2009, Åbo Akademi University, Turku, p. P18.

LIST OF ABBREVIATIONS

Ac	acetyl
Ar	aryl
BINOL	1,1'-Bi-2-naphthol
Bn	benzyl
Bu	butyl
CONI	conidendrin
Cp	cyclopentadienyl
Cy	cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DFT	density functional theory
DHF	dihydrofurane
DHP	dihydropyrane
DIBAL-H	diisobutylaluminium hydride
DIOP	O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DMF	dimethylformamide
ee	enantiomeric excess
Et	ethyl
GC	gas chromatography
HF	Hartree–Fock method
HMR	7-hydroxymatairesinol
HPLC	high performance liquid chromatography

iBu	isobutyl (2-methylpropyl)
iPr	isopropyl (2-methylethyl)
IUPAC	International Union of Pure and Applied Chemistry
LAH	lithium aluminium hydride
Me	methyl
MM	molecular mechanics
MOM	methoxymethyl
MR	matairesinol
Ms	mesyl
Naph	naphthyl
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Ph	phenyl
Piv	pivaloyl (tertbuthylformyl)
Pr	propyl
RT	room temperature
TADDOL	α,α,α',α'-tetra(aryl)-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol
TBDMS	tert-Butyldimethylsilyl
TFA	trifluoroacenic acid
THF	tetrahydrofurane
TMS	trimethylsilyl
Ts	tosyl (4-methyl-phenyl-sulphonyl)

Table of Contents

1. INTRODUCTION

Finland has a long tradition of utilizing forests, especially for production of pulp and paper. However, in new biorefinery concepts, the tree should be used also for production of fuels, materials and fine chemicals. One emerging and highly promising area is the isolation and utilization of lignans from wood knots. In fact, the isolation and utilization of lignans has already made much progress and the most abundant lignan hydroxymatairesinol is already used as a health beneficial dietary supplement, and development of hydroxymatairesinol as a natural antioxidant is ongoing. However, hydroxymatairesinol is also a valuable optically pure compound, which could be utilized in high-value applications in the field of organic chemistry.

Preparation of chirally pure compounds is one of the main tasks of modern organic chemistry. One of the simplest ways to obtain optically pure chiral compounds is to isolate and/or derivatize natural products. However, this so-called ´chiral pool´ approach works only for a limited number of compounds. A more effective approach is to use the chirality of natural compounds to induce secondary chirality in the target molecule. In this case, the chirality of natural compound can be utilized for preparation of a series of chiral compounds and the source natural molecule could be recovered from the product mixture and used once more.

A number of enantiopure compounds from natural sources have been used as chiral auxiliaries in stereoselective reactions, derivatization agents for separation of enantiomers, or as ligands for asymmetric catalysis in organic synthesis.

For example, chiral diols obtained from tartaric acids[1] or phosphorous based ligands derived from carbohydrates[2], have shown excellent results as ligands in transition metal catalyzed asymmetric synthesis.

Lignans are a class of natural compounds which are defined by the union of two phenyl propane units or their biogenetic equivalents. These compounds are optically pure and often biologically active.[3] Hydroxymatairesinol (HMR) is the most abundant lignan in Norway spruce (*Picea abies*). The knots, i.e. the part of the branch that is embedded in the stem, normally contain about 10% of HMR.[4]

Since the discovery of large amounts of HMR in the wood knots (year 1998), by the group of Prof. Holmbom, this compound has been extensively investigated by Finnish researchers.

1.1 Lignan hydroxymatairesinol –natural sources, isolations and chemical properties

The first report concerning lignans in wood was published in 1892 by Lindsey and Tollens.[5] They found that specific substances could be extracted from spent liquor of sulphite pulping of the Norway spruce (Picea abies) wood. However, the structures of the isolated compounds were not resolved until the publications of Erdtman in 1934[6] and Haworth in 1935[7,8] and 1936.[9] In these publications, the structures of matairesinol and conidendrin lignans were described (Figure 1). In 1936 [9] Haworth also proposed the name "lignans" to the family of compounds defining as a class of compounds derived from two β-β'-linked phenylpropane units. This definition is still valid according to IUPAC recommendations from 2000.[10]

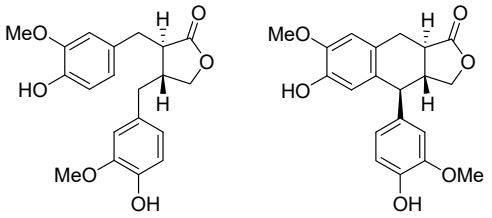


Figure 1. Structure of the lignans Matairesinol and Conidendrin.

In 1957,[11] Freudenberg and Knof reported the isolation of hydroxymatairesinol (HMR) and several other lignans from the Norway spruce wood material. They also proposed a structure of HMR and the presence of two isomers of this compound.

During the subsequent several decades of extensive research in the area, many lignans were isolated and identified,[3] but lignans were still minor substances which were difficult to isolate until the finding at Åbo Akademi in the late 1990s. Holmbom and co-workers[12] determined that the knots of the Norway spruce, i.e., the branch bases inside the stems of trees, contained around 10% of lignans. It was previously reported that high concentration of extractives in knots can be found[13], however, the extractives were not analyzed in details. The knots are not very valuable in the manufacturing of pulp. Actually, knots can be considered detrimental for pulping and the pulp quality and should preferably be separated before pulping. Therefore, a wood knot separation process has been developed in the Laboratory of Wood and Paper Chemistry at Åbo Akademi University. It turns out that wood knot particles have a higher density and could be separated, after the appropriate grinding, by sedimentation in water.[14,15]

Detailed analysis of the Norway spruce knot extracts showed that the content of lignans in the Norway spruce knots was between 6 and 24%. The main component of the knot extractives was HMR and content varied between 65 and 85% (Figure 2).[4]

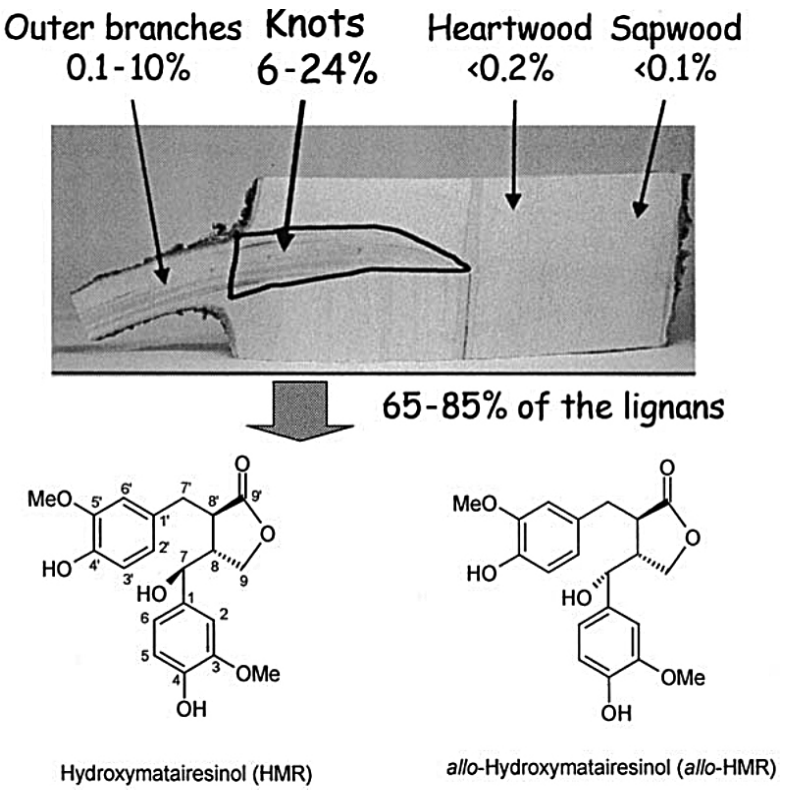


Figure 2. Typical concentrations of lignans, excluding oligolignans, in the Norway spruce tree stem, and the structure of the two isomers of the predominant lignan, 7-hydroxymatairesinol.

It was shown that naturally occurring HMR consisted of two diastereomers in the ratio of 3:1 and that the major isomer had the 7S,8R,8'R configuration, while the minor isomer called 7-allo-hydroxymatairesinol had the 7R,8R,8'R configuration (Figure 2).[16]

After the wood knots separation process had been developed, the isolation of pure HMR was optimized. The ethanol extraction of the Norway spruce knot material gave a mixture highly enriched with HMR (~70%). HMR was precipitated directly from the ethanol extract by addition of potassium acetate.[11,17] It is interesting to notice that the precipitation affects only the major diastereomer of HMR, allo-HMR stays untouched in mother liquor.

Binding together these facts with statistics of the Finnish paper industry, Bjarne Holmbom et al.[12] calculated the amount of pure HMR, which could potentially be

produced in one of the Finnish paper mills. Using about 1000 tons of spruce wood per day, the paper mill could produce about 600 kg of HMR. Assuming a yield of 60%, this would mean a production of pure HMR (90-95%) of 360 kg per day which corresponds to 130 tons per year. Therefore, it can be concluded that the technology for production of hundreds tons of pure HMR per year has been developed.

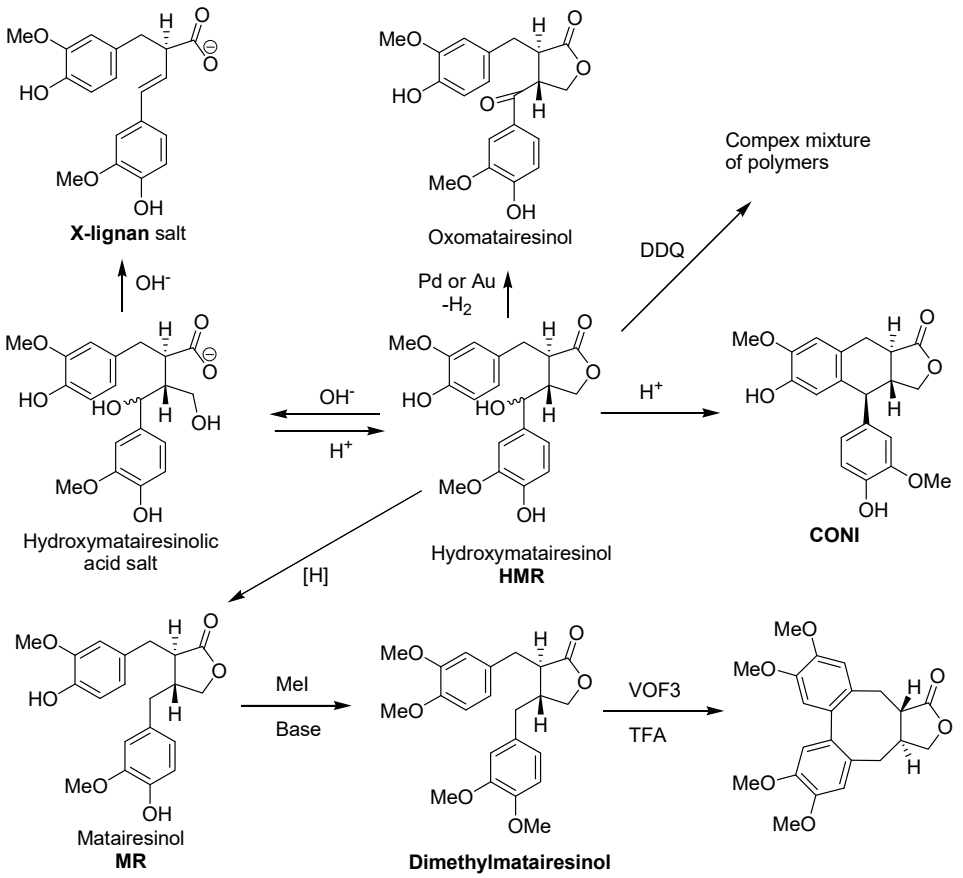
Due to the discovery of the large amounts of HMR in the wood knots and development of the biorefinery processes in wood industry, HMR became readily available and development of applications for utilization of the compound is very important. It already found application as a food additive (approved by the FDA USA)[18] and the antioxidantive properties of the molecule are now under investigation.[19] Oxomatairesinol was prepared from HMR and found the application as a UV absorbing agent in Sunscreen.[20]

HMR and its derivatives have shown other interesting biological properties. For example, anticancer activity of HMR has been reported for prostate cancer and breast cancer models.[21] Anti-inflammatory properties of HMR have been described recently.[22,23] Hepatoprotective activity has been reported for HMR-glycoside and other 7-hydroxy-lignan-glycosides.[24] A number of hydroxymatairesinol derivatives also showed significant anti-cancer activity.[25,26]

1.1.1 Chemical properties of hydroxymatairesinol

Hydroxymatairesinol has several functionalities which determine its properties which are illustrated at scheme 1. The two aryl groups are very electron rich and therefore they could easily react with electrophiles or with oxidants.

The 7-hydroxyl group is located on the benzylic position and could be easily eliminated either in acidic or in alkaline conditions because of the para-hydroxyl substituent of aryl group. The sensitivity of the 7-hydroxy group determines the presence of two diastereomers of HMR in the ratio of 3:1. The lactone ring could undergo transesterification in acidic and basic conditions. The two chiral centers on the lactone (8R and 8'R) are quite stable. However, the alpha position of the carboxylic acid function could be slowly racemized in strong basic conditions.



Scheme 1. Chemical transformations of the HMR.

In acidic conditions HMR undergoes cyclization to conidendrin (**CONI**).[11] Mild basic conditions lead to the hydrolysis of the lactone and the formation of the salt (Hydroxymatairesinolic acid salt).[27] In strong basic conditions the molecule converts to substance '**X-lignan**' via retro-condensation.[28] The 7-hydoxyl group was shown to be easily eliminated in reductive conditions to give matairesinol (**MR**), for example by hydrogenolysis on palladium[11] or by sodium borohydride.[29] Oxidative conditions usually lead to the polymerization of the HMR because of the free phenolic hydroxyls and the sensitive 7-hydroxy group.[30] However, matairesinol with protected phenolic groups (methylated by methyl iodide) could be oxidatively coupled to form an 8-membered ring structure.[31] **HMR** could also be dehydrogenated by palladium or gold catalyst to give 7-oxomatairesinol.[32,33]

The possibility of using extract of the Norway spruce knots as a starting material for preparation of fine chemicals would be attractive. The extract could be used for isolation of HMR (by precipitation of potassium acetate adduct or

chromatographically). The extract could be directly used for a high yield preparation of conidendrin by the acidic treatment with the subsequent crystallization of the pure conidendrin.

Furthermore, the highly functionalized structure of the lignans (i.e. lactone ring, phenolic groups, electron rich aryls) and the presence of several pure chiral centers gives plenty of possibilities to derivatize the molecules into potentially interesting chiral auxiliaries, ligands for asymmetric catalysis or organocatalysis.

1.2 Enantioselective synthesis as a powerful tool for preparation of chiral compounds

There are three usual strategies to prepare a chiral compound in synthetic chemistry:

1) The chiral pool synthesis – use of readily available natural enantiopure substances for preparation of complex enantiopure chemical compounds. Using regular chemical transformations but preserving the built in chirality.

2) Resolution of enantiomers – preparation of desired compounds by nonselective chemical transformations and then separation of the desired enantiomer by co-crystallization with chiral compounds or chiral chromatographic methods or by other separation techniques.

3) Enantioselective synthesis – use of an auxiliary chiral compound to make the reaction diastereoselective and get only the desired isomer after separation of the auxiliary.

The first and second strategies have inherent disadvantages. The first strategy is limited by the amount of source 'chiral pool' molecules available. With the second strategy one can get a maximum 50% yield of the desired molecule.

Enantioselective synthesis lacks these disadvantages and the development of asymmetric synthetic methods gives excellent pathways to prepare the desired chiral compounds.

To provide selectivity in asymmetric reactions it is most important to create the asymmetric environment around the reaction center. This asymmetric environment of non-chiral molecules could be created by attaching of the chiral auxiliary. The auxiliary could then be detached after the reaction.

If the sequence: attaching of the chiral molecule – stereoselective reaction – detaching of the auxiliary is performed simultaneously, the reaction is becoming catalytic. In this

case, the amount of the auxiliary could be significantly decreased from the stoichiometric ratio. This approach called `Asymmetric catalysis` appears to be the most efficient and atom economic to prepare certain chiral molecules.

Thus, to successfully develop an asymmetric catalysis we need to determine which parameters the chiral catalyst should fulfill.

First of all, the catalyst should have an asymmetric environment. The catalyst should also provide enough space to bind the substrates and form a transition state for the reaction. The transition state should be sufficiently sterically hindered to ensure stereoselectivity of the proceeding reaction.

Bidentate chelate ligands with hindered structures and preferably *C2* symmetry are good candidates for the use in asymmetric catalysis.

For example when Ti-TADDOLate complex catalyze the $ZnEt_2$ addition to benzaldehyde[34] the TADDOL ligand provide hindered structure with a catalytic site accessible from only one enantioface (Figure 3). A C_2-symmetry of the complex promotes 2 identical places of binding which increase the efficacy of the catalyst.

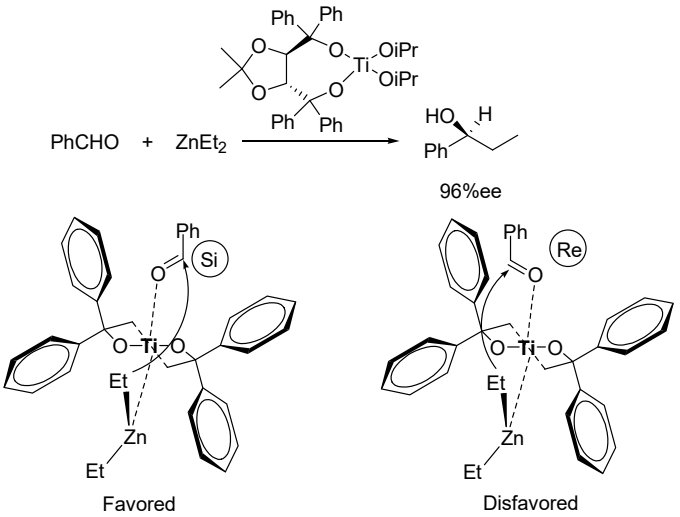


Figure 3. Mechanism of the enantioinduction in $ZnEt_2$ addition to benzaldehyde catalyzed by Ti-TADDOLate

For more detailed discussion of the requirements for asymmetric induction by TADDOL, see section 2.Results and discussion.

1.2.1 Chiral 1,4-diols as a tool in asymmetric synthesis

I will start the description of chiral ligands with diols because the chiral diols could not only be used as ligands, organocatalysts or auxiliaries but also as a source of chiral diamines[35], diphosphines[36–38] etc.

A variety of 1,4-diols have been found to be excellent chiral inducers in different types of asymmetric transformations. The main representatives of chiral 1,4-diols are two classes of the compounds – TADDOLs and BINOLs (Figure 4).

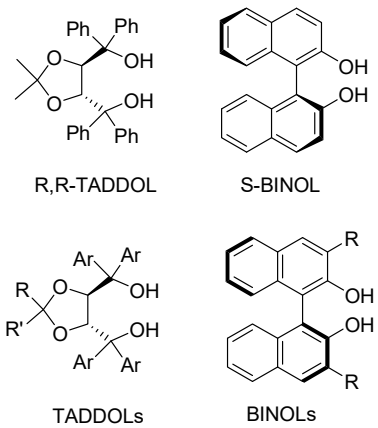


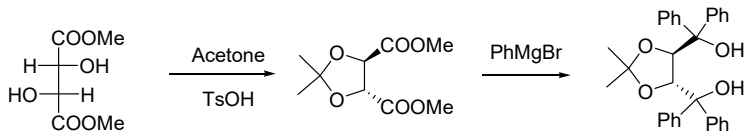
Figure 4. TADDOLs and BINOLs.

Due to the rigidity of the structures and effective shielding of certain enantiofaces these compounds and their derivatives showed excellent enantioinduction in different reactions.[1,39]

Herein only aliphatic 1,4-diols will be described and BINOLs will be left out of the scope of this review.

1.2.1.1 Syntheses of chiral 1,4-diols

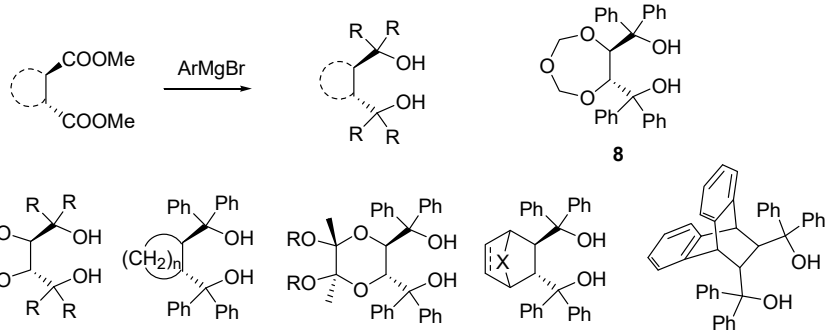
Most of the chiral diols which were applied in asymmetric catalysis have been derived from tartaric acid. These compounds have a collective name – TADDOLs which originated from the first prepared compound of the class – α,α,α´,α´-**T**etra**a**ryl-2,2-dimethyl-1,3-**d**ioxolan-4,5-**d**imethan**ol** (TADDOL, Figure 4). This molecule was prepared in the Dieter Seebach laboratory by Albert Beck in 1982[40] by reacting dimethyl tartrate with acetone to give cyclic ketal followed by reaction with excess of phenylmagnesium bromide (Scheme 2).



dimethyl-L-(R,R)-(+)-tartrate R,R-TADDOL

Scheme 2. Preparation of the TADDOL structure.

Later a broad series of the TADDOLs using the same route (Scheme 2) but with variation of the ketone and Grignard reagent were synthesized (Scheme 3). Some compounds similar to TADDOLs, not derived from the tartaric acid, were also synthesized using esters of appropriate diacids as starting materials (Scheme 3).



TADDOLs
R = Ar or Alkyl

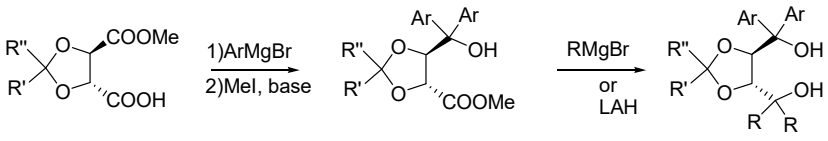
n=1 **1**
n=2,3 **2(a,b)**
n=4 **3**

R=Me, Et 4(a,b)

X= CH_2 **5(a,b)**
X=$(CH_2)_2$ **6(a,b)**
X= O **7**

Scheme 3. Preparation of TADDOLs and similar compounds. TADDOLs[41–45]; 1[46]; 2, 3[47]; 4[48]; 5[49]; 6[50]; 7[47]; 8[34]; 9[51].

Using monoesters of the diacids as the starting materials, a number of unsymmetrical TADDOLs were prepared.[52,53] The first reaction of the monoester leaves the free acid function unreacted and after esterification the other two substituents could be added (Scheme 4).

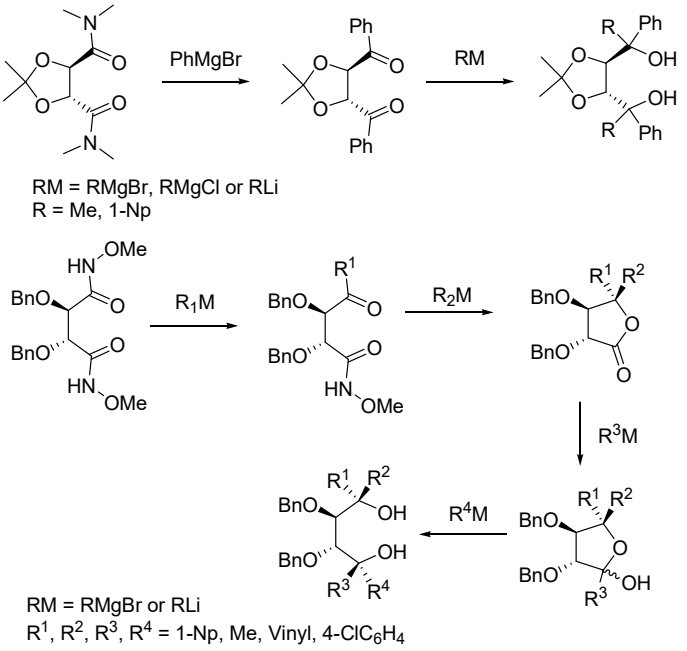


R = Ar, Alkyl or H

Scheme 4. Preparation of unsymmetrical TADDOLs.

It is necessary to mention that the TADDOLs and TADDOL-like compounds with different aryl/alkyl substituents were also prepared by stepwise addition of the

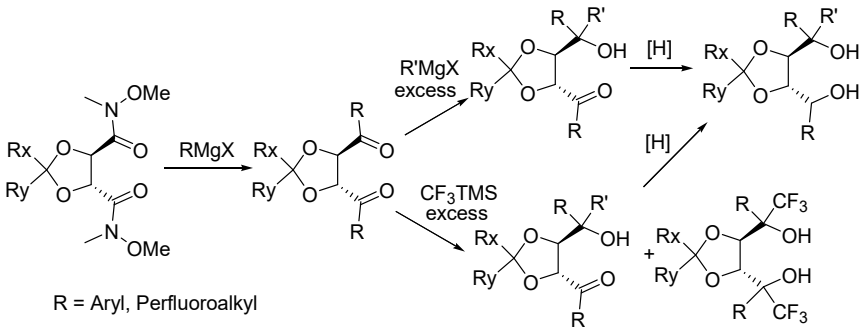
substituents (Scheme 5). Using amides of the appropriate diacid as a starting material it was possible to introduce not only two different substituents[47], but also four different substituents with stereo-control of the formed stereocenters[54].



Scheme 5. Preparation of TADDOLs and TADDOL-like compounds with different aryl/alkyl substituents.

It is noteworthy that R^2M in the case of dibenzyl-derivative reacts to the ketone, but not to the Weinreb amide in contrast to the TADDOL structure where phenylmagnesium bromide reacts first with both amide groups to form a diketone (Scheme 5).

Using diacids Weinreb amides as starting materials a number of different tri-substituted TADDOLs were prepared (Scheme 6).[55,56] The publications also report significant difficulties to introduce the 4th substituent.



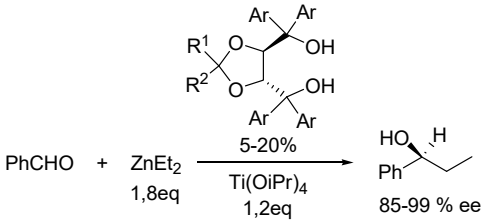
Scheme 6. Preparation of the tri-substituted TADDOLs.

Tetra-substituted TADDOLS were obtained only in case of di-Ph-di-CF_3-TADDOL and tetra-C_4F_9-TADDOL.

1.2.1.2 Applications of TADDOL-type chiral 1,4-diols in asymmetric synthesis

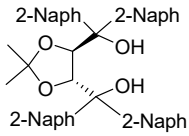
Nucleophilic additions to C=O double bonds

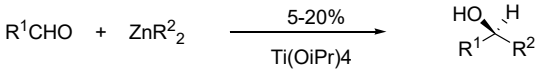
When the original TADDOL was synthesized it found its first application as a ligand in alkylation of aldehydes by alkyl-trialkoxytitanium.[40] Later the catalytic method of alkylation of carbonyl compounds by diethylzink catalyzed by titanium TADDOLates was developed (Scheme 7).[34]



Scheme 7. Catalytic asymmetric diethylzinc addition to benzaldehyde catalyzed by Ti-TADDOLates.

The method showed impressive selectivity. It was determined that TADDOL with bulky aryl groups catalyzed the reaction more selectively. At the same time, influence on the selectivity of R^1 and R^2 substituents (Scheme 7) was minimal. The method was applied to many different carbonyl compounds and alkyl/aryl-zink reagents with different Ti-TADDOLate catalysts. Several examples are presented in Scheme 8.





R^1	R^2	ee, %
Ph	Et	99
Cy	Et	99
1-Propenyl	Et	99
1-cyclopentenyl-1	Et	99
Hexyl	Et	99
Ph	Isomayl	99
Ph	Vinyl	92
Ph	$-(CH_2)_6OMOM$	98
4-NO_2-Ph	Ph	98
2-TMS-ethynyl	Me	98
iPr	Me	95

Scheme 8. Several examples of the catalytic asymmetric dialkylzinc addition to aldehydes catalyzed by Ti-TADDOLates.[34,47,57–59]

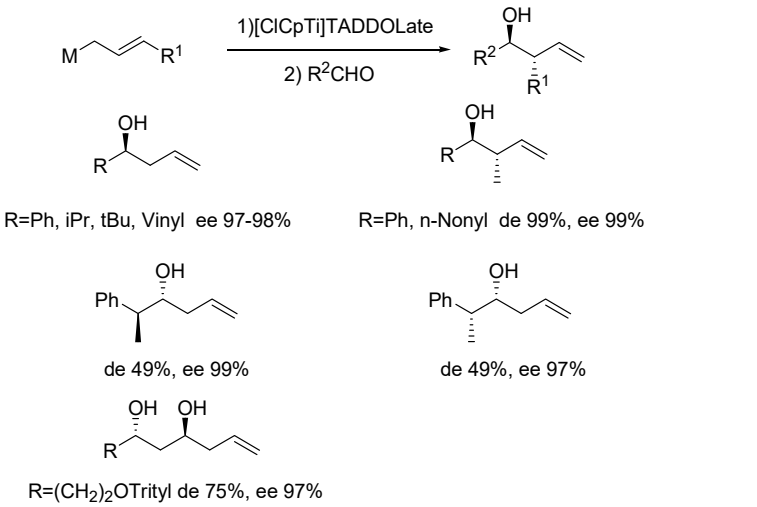
When perfluorinated TADDOLs were applied to the reaction, these catalysts showed an unprecedented activity combined with an excellent enantioselectivity of up to 98% ee.[55,60]

Trialkylaluminium compounds were also used for alkylation of carbonyl compounds catalyzed by titanium TADDOLates.[61]

Ti-TADDOLates have found application in total synthesis. Using the above mentioned method, macrolactin A, a macrolide antibiotic having strong activity against B16-F10 murine tumor cells and HIV-1, was prepared.[62]

It is also worth mentioning that heterogeneous TADDOL catalysts were prepared. The TADDOL structure was bound to a polymer support and the catalyst became reusable.[63–66]

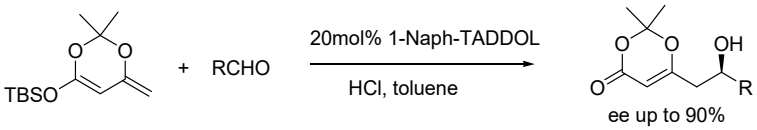
The allylation of aldehydes and ketones, leading to products with the maximum of two new stereocenters and diverse functionalities, is an important example of acyclic stereocontrol. TADDOLs were shown to be excellent ligands in asymmetric allylations of aldehydes. Thus, the enantioselective transfer of the allylic group from allyl-lithium or Grignard reagent to the aldehyde by CpTi-TADDOLate provided the corresponding homoallylic alcohol with the excellent diastereo- and enantioselectivity (Scheme 9).[67,68]



Scheme 9. Asymmetric allylation of aldehydes by AllylCpTiTADDOLates.

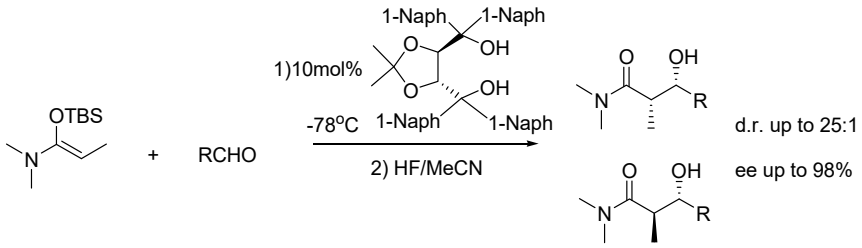
Aldol reactions

The asymmetric aldol reaction is one of the most important topics in modern organic synthesis. A new class of catalytic asymmetric aldol reactions has recently been developed using organocatalysts.[69] TADDOLs and their derivatives have also been shown to be effective as organocatalysts. For example, the Mukaiyama aldol reaction has proven to be a powerful tool for complex structure synthesis, and in 2005, Gondi et al. reported the use of 1-Naph-TADDOL as the organocatalyst in the vinylogous Mukaiyama aldol reaction of silyl dienol ethers with a series of aldehydes.[70] The products were obtained in good to excellent yields and with ee values up to 90% (Scheme 10).



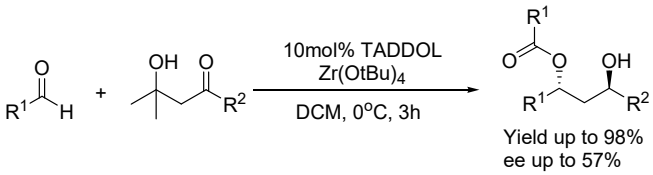
Scheme 10. Asymmetric vinylogous Mukaiyama aldol reaction.

In 2006, a highly diastereo- and enantioselective Mukaiyama aldol reactions of O-silyl-N,O-ketene acetals with aldehydes catalyzed by 1-Naph-TADDOLs were developed.[71] The reaction was effective for a number of aldehydes, giving the corresponding chiral amide products in good to excellent yields and selectivities (Scheme 11).



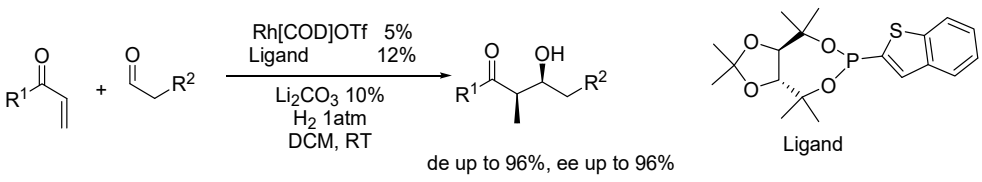
Scheme 11. Asymmetric Mukaiyama aldol reaction.

In addition to organocatalytic aldol-type reactions, Schneider et al. reported Zr-TADDOLate catalyzed enantioselective aldol-Tishchenko reactions.[72] The zirconium-TADDOLate complex was found to promote the reaction of the ketone aldol adducts with a range of aldehydes, providing 1,3-diol monoesters in good to excellent yields, complete diastereocontrol and with up to 57% ee (Scheme 12).



Scheme 12. Asymmetric Zr-TADDOLate catalyzed aldol-Tishchenko reaction.

In 2008, Krische et al. reported the first enantioselective reductive aldol couplings of vinyl ketones.[73] It was catalyzed by rhodium complexes with a new class of TADDOL phosphonite ligands. The reductive aldol coupling of methyl vinyl ketone or ethyl vinyl ketone with aldehyde allowed the corresponding linear aldol adducts to be obtained with high diastereo- and enantioselectivities of up to 96% de and 96% ee respectively (Scheme 13). It should be mentioned that much higher yield and selectivity was obtained when using tetramethyl-TADDOL phosphonite ligand than using normal tetraphenyl-TADDOL derivative.

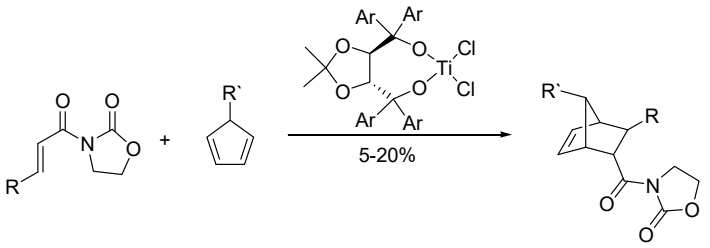


Scheme 13. Asymmetric reductive aldol couplings of vinyl ketones.

Cycloadditions 2+4, 3+2, 2+2+2, 1+2

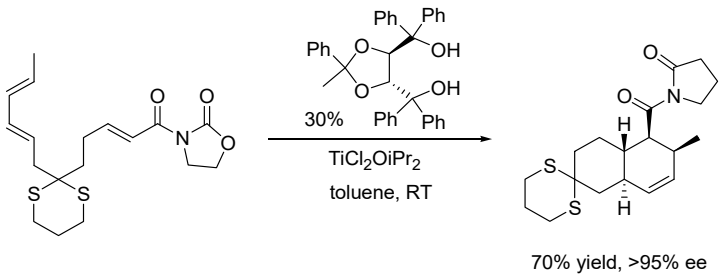
4+2 Cycloadditions

Chiral 1,4-diols such as TADDOLs have been demonstrated as excellent chiral ligands in enantioselective Diels–Alder reactions.[74] For example, Diels–Alder reactions of enoyl-oxazolidinones of fumaric, acrylic, and crotonic acids with cyclopentadiene led almost quantitatively to a single stereoisomer by using (R,R)-TADDOLs as ligands of $TiCl_2(Oi\text{-}Pr)_2$ (Scheme 14).[44,75–79]



Scheme 14. Asymmetric Diels-Alder reaction of enoyloxazolidinones with cyclopentadiens.[75–78]

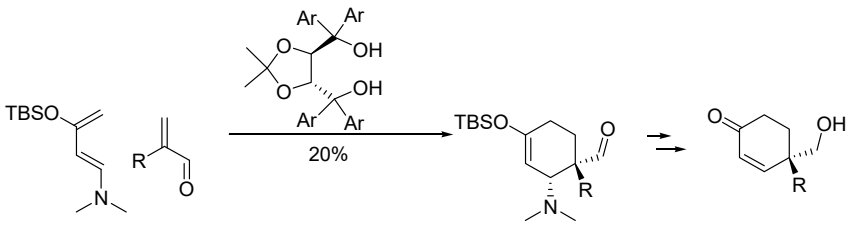
Enoyloxazolidinones were also reacted with dienes under similar conditions providing the cycloaddition products with excellent enantioselectivities of up to 99% ee.[80]



Scheme 15. Asymmetric intramolecular Diels-Alder reaction of enoyloxazolidinone-diene.[80]

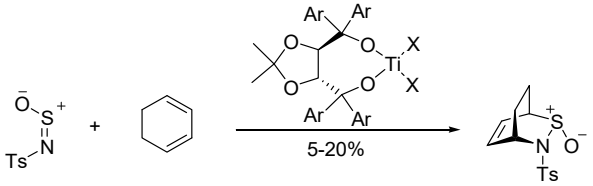
Other α,β-unsaturated carbonyl compounds, such as phenylsulfonylmethyl enones [81,82], ene-1,2-diones [83,84], quinines [85,86], amidoacrylates [87] and maleimides[88]were also utilized in the Diels-Alder reaction with Ti-TADDOLate catalysis, leading in most of the cases to enantiopure products.

Until recent years, examples of Diels-Alder reaction promoted by organocatalyst were not known. In 2004, Rawal et al. reported an example of using TADDOLs as the organocatalysts for the Diels–Alder reaction of aminosiloxydienes with acrolein dienophiles to afford the corresponding products in good yields and high enantioselectivities (Scheme 16) [89].



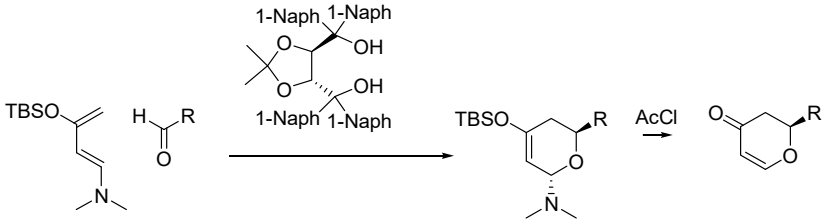
Scheme 16. Asymmetric organocatalytic Diels-Alder reaction.[89]

The hetero-Diels–Alder reaction has attracted much interest during the last decades because it provides an easy approach towards six-membered partly saturated heterocycles.[90] The hetero-Diels–Alder reactions of cyclohexadiene with N-sulfinyl dienophiles promoted by titanium TADDOLates have been reported by Bayer et al. in 2002.[91] In almost all cases, the cycloadditions resulted in endo-products, which were obtained with up to 83% yield and 69% ee.



Scheme 17. Asymmetric hetero-Diels-Alder reaction.[91]

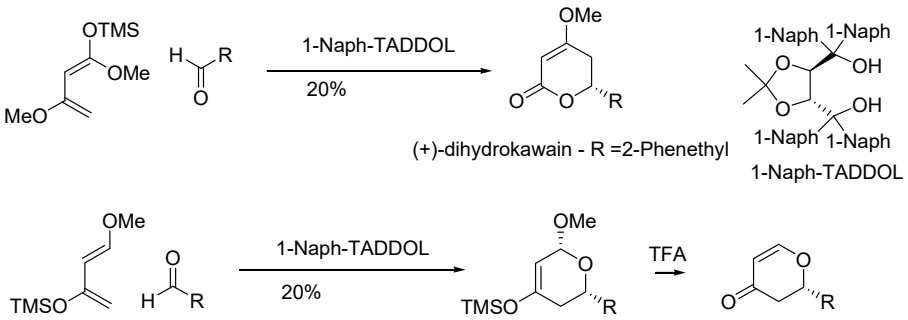
In addition, several organocatalytic hetero-Diels–Alder reactions have been reported. The 1-Naph-TADDOL was employed as the organocatalyst to promote the reaction of 1-amino-3-siloxybutadiene with aldehydes.[92] The reaction provided the cycloadducts with high enantioselectivity (Scheme 18).



Scheme 18. Asymmetric organocatalytic hetero-Diels-Alder reaction.[92]

TADDOLs were also used by Zhang et al. to catalyze the hetero-Diels–Alder reaction of an aldehyde with Brassard's diene, affording the corresponding chiral δ-lactone derivative with enantioselectivities of up to 98% ee (Scheme 19). The natural product (+)-dihydrokawain was prepared with high enantioselectivity to show the significance

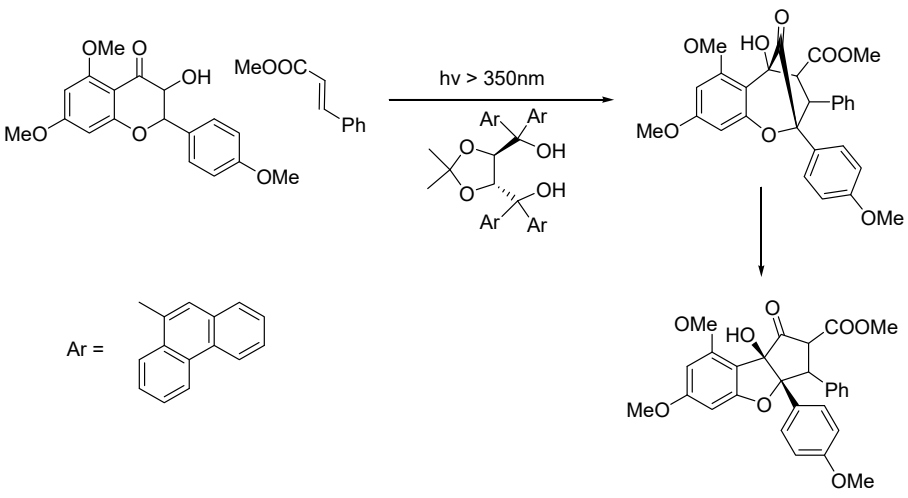
of this method.[93] In 2006, the same group reported hetero-Diels–Alder reactions of Danishefsky's diene and analogs with various aldehydes catalyzed by TADDOL and its derivatives (Scheme 19).[94] The 1-Naph-TADDOL showed in most of the cases high enantioselectivities of 76–98% ee.



Scheme 19. Asymmetric organocatalytic hetero-Diels-Alder reaction of Brassard's and Danishefsky's dienes with aldehydes. [93,94]

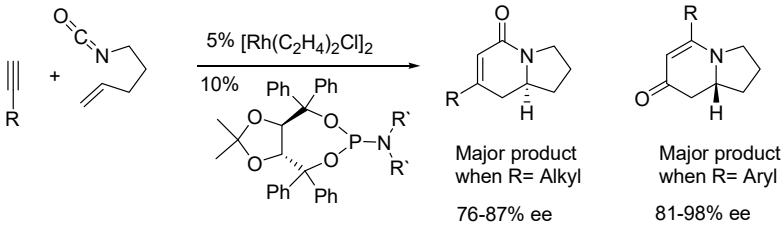
3+2 Cycloadditions

TADDOLs have also been demonstrated to be excellent promoters of asymmetric 1,3-dipolar cycloadditions.[95] In 2006, Gerard et al. reported a synthesis of chiral Rocaglamides based on [3 + 2] dipolar cycloaddition of an oxidopyrylium betaine and methyl cinnamate, using phenantrenyl-(9)-TADDOL as organocatalysts (Scheme 20).[96] The photocycloaddition adduct was prepared in 61% yield and was further converted into methyl rocaglate with 82% ee.[97]



Scheme 20. [3 + 2] dipolar cycloaddition catalyzed by phenantrenyl-(9)-TADDOL.[96,97]

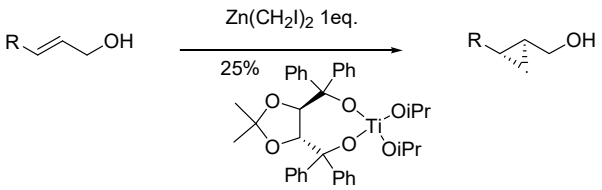
In 2006, Yu and Rovis developed a selective Rh-catalyzed [2+2+2]-cycloaddition method using TADDOL-derived phosphoramidites as chiral ligands (Scheme 20).[98] The alkenyl isocyanates were reacted with terminal alkynes to afford the corresponding bicyclic lactams or vinylogous amides. The cycloaddition proceeded with high yields, regio- and enantioselectivities. The applicability of the methodology was demonstrated in a total synthesis of (+)-lasubine II.[99]



Scheme 21. [2+2+2] cycloaddition catalyzed by Rh-TADDOL-phosphoramidite complex.[98,99]

1+2 Cycloadditions

In 1995, Charette et al. reported asymmetric cyclopropanation of allylic alcohols promoted by Ti-TADDOLates (Scheme 22).[100] Excellent enantioselectivities of up to 98% ee were achieved. In 2001 the scope of the methodology was extended to provide cyclopropane products in moderate to excellent yields (63-90%) and enantioselectivities (48-94% ee) (Scheme 22).[101]



Scheme 22. Cyclopropanation reaction catalyzed by Ti-TADDOLates.[100,101]

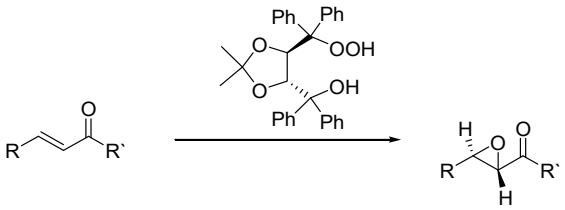
To improve the versatility of the method a new family of chiral phosphates derived from TADDOL was developed.[102] The use of these ligands in the Simmons-Smith cyclopropanation of both functionalized and unfunctionalized olefins led to the formation of the desired cyclopropanes in good yields and moderate enantioselectivities (31–75% ee).

Oxidations

Many biologically active compounds have an epoxide functional group.[103] This group is also very useful in versatile building blocks. Therefore the development of asymmetric

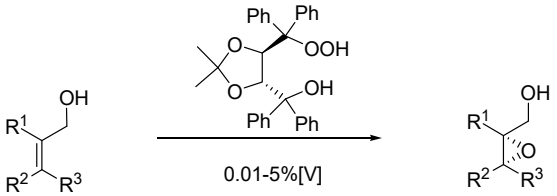
epoxidation of olefins is an important and challenging task in modern organic chemistry.[104]

In 2001, Seebach and Aoki reported the preparation of a TADDOL-derived hydroperoxide TADDOOH.[105] This peroxide appeared to be relatively stable and was utilized as a chiral oxidative agent for several asymmetric oxidations. For example, the treatment of a series of enones with TADDOOH pre-deprotonated by strong base (BuLi or DBU/LiCl) affords the corresponding epoxy ketones in high yields and enantioselectivities between 40–97% ee (Scheme23).



Scheme 23. Epoxidation of enones by TADDOOH.[105]

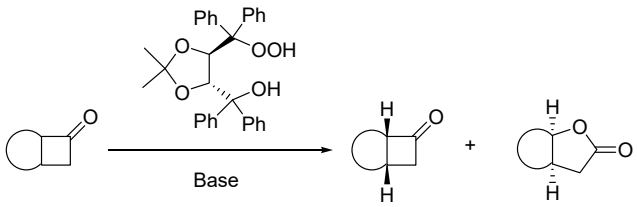
In 2003 vanadium(V)-catalyzed epoxidation of allylic alcohols in the presence of TADDOOH was reported (Scheme 24).[106] A series of chiral epoxides was prepared with moderate enantioselectivities (41–72% ee). Similar epoxidations were also catalyzed by achiral oxovanadium(IV)-substituted polyoxometallate (POM) (Scheme 24).[107] Oxidations of allylic alcohols by TADOOH furnished a good yield of epoxyacohols with variable enantioselectivities (18–90% ee).



Scheme 24. Epoxidation of enones by TADDOOH catalyzed by vanadium.[106,107]

The TADDOOH was also applied as an oxidant in enantioselective oxidation of sulfides. The methyl phenyl sulfide was directly oxidized to the corresponding (S)-sulfoxide in 73% yield and 86% ee.[105]

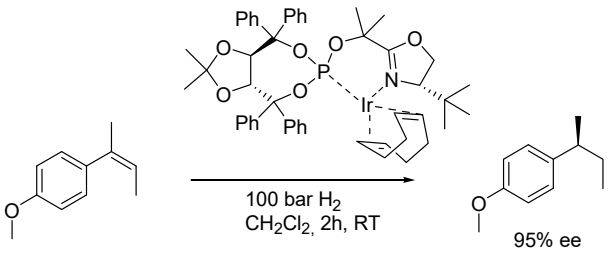
In addition, this oxidant was applied to the asymmetric Baeyer-Villiger oxidation of racemic cyclobutanones.[105] The cyclobutanones were oxidized into the normal Baeyer-Villiger products, at the same time unreacted cyclobutanones were enantiomerically enriched up to 99% ee.



Scheme 25. Enantiospecific Baeyer-Villiger oxidation of racemic cyclobutanones by TADDOOH.[105]

Reductions

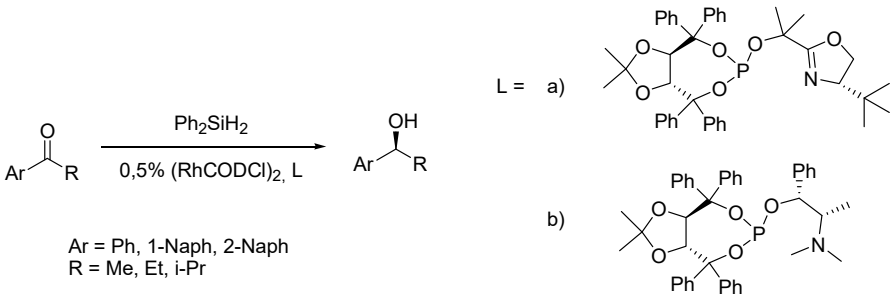
The enantioselective hydrogenation of olefins with chiral rhodium, ruthenium or iridium catalysts is nowadays a widely used method in asymmetric catalysis.[108] However, enantioselective hydrogenation of unfunctionalized olefins is still a particularly difficult task. Because of a polar group being close to the double C=C bond the olefin can coordinate to the metal catalyst and therefore provide a high catalytic activity and enantioselectivity. Pfaltz et al. reported a new iridium hydrogenation catalysts which showed exceptionally high activity with unfunctionalized olefins and, in many cases, excellent enantioselectivity of up to 95% ee (Scheme26).[109]



Scheme 26. Enantioselective iridium-catalyzed hydrogenation of unfunctionalized olefins.[109]

However, several non-TADDOL based iridium catalysts were described lately which showed better activities and selectivities in similar applications.[110]

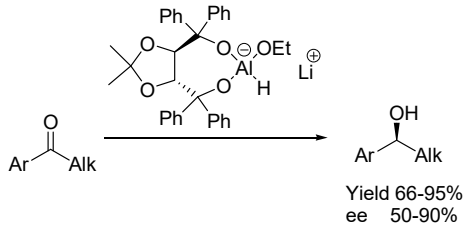
The ligand was also successfully used for rhodium catalyzed hydrosilylation of ketones by Seebach and Heldmann.[111] Enantioselectivities up to 95% ee were obtained (Scheme 27(a)).



Scheme 27. Enantioselective rhodium-catalyzed hydrosilylation of ketones.[111,112]

Finn et al. reported a chiral phosphite P,N-ligand derived from TADDOL and (+)-N-methylephedrine. The Rh-catalyzed hydrosilylation of ketones using this ligand provided a high level of asymmetric induction (15–89% ee) (Scheme 27(b)).[112]

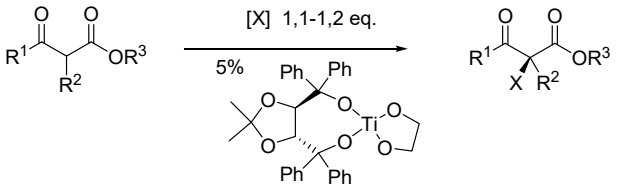
In addition, a non-catalytic reduction of ketones by lithium aluminium hydride functionalized by TADDOL has also been reported. Seebach and Beck reported this method for the reduction of arylketones with high yields and stereoselectivities (Scheme 28).[113]



Scheme 28. Enantioselective reduction of Aryl-Alkyl-ketones.[113]

Alpha halogenations of carbonyl compounds

It is known that organo-fluorine compounds are extremely rare in nature.[114] Nevertheless, fluoro-containing compounds are becoming very important in medicinal chemistry because of their special effects on bioactivity.[115] TADDOLs have been shown to be useful in asymmetric fluorinations. For example, Hintermann et al. reported enantioselective catalytic fluorination of β-ketoesters performed by F-TEDA (N-chloromethyl-N`-fluoro- Triethylenediamine tetrafluoroborate) as the fluorinating agent in the presence of a Titanium-TADDOLate catalyst. The fluorinated substances were obtained in high yields (85–95%) and stereoselectivities up to 90% ee were achived (Scheme 29).[116,117]



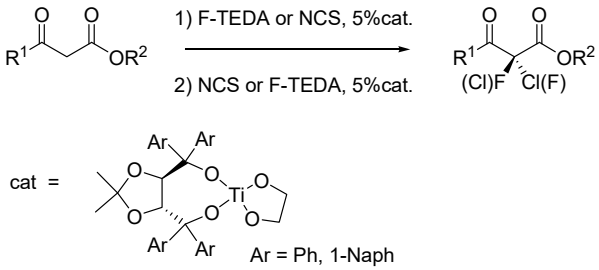
[X] = F-TEDA, NBS, NCS
X = F, Br, Cl

R^1 = Ph, Et, Me
R^2 = Me, H, Bn
R^3 = Et, Ph_2CH, Bn, 1-Naph, 2,6-(t-Bu)$_2$-4-Me-C_6H_2, 2,4,6-(i-Pr)$_3C_6H_2$

Scheme 29. Asymmetric halogenation of β-ketoesters catalyzed by Ti-TADDOLates.[116,117]

The same group also developed similar methods for chlorination (with N-chlorosuccinimide) and bromination (with N-bromosuccinimide) of β-ketoesters. The method provided high yields (83-97%) and comparable enantioselectivities (up to 88% ee) (Scheme 29).[118] The method was examined on a broad scope of substrates using different fluorinating agents.[119,120] Crystallization of the intermediate of the reaction showed the mechanism and the stereocontrol of the reaction.[121]. Titanium complex, which was isolated and crystallized bore TADDOL and two dicarbonyl molecules and only one side was open for the attack in each of the dicarbonyl molecules[121]

This methodology was also extended for one pot hetero-dihalogenation (chlorination and fluorination) of β-ketoesters providing the corresponding chloro-fluoro-β-keto esters with enantioselectivities up to 65% ee.[122]

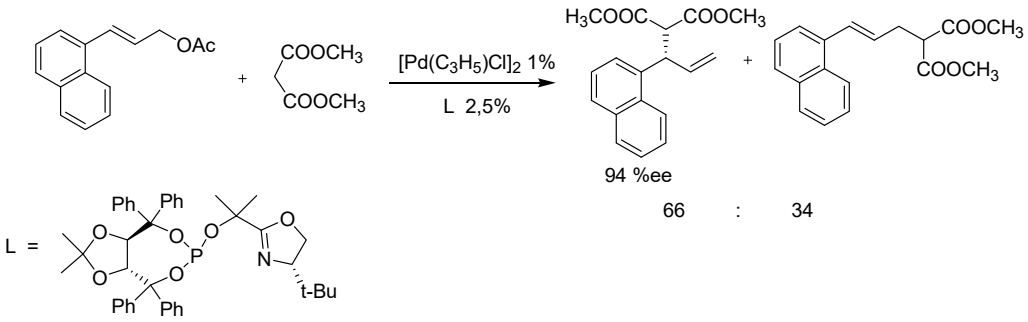


Scheme 30. Asymmetric fluorochlorination of β-ketoesters catalyzed by Ti-TADDOLates.[122]

Allylic substitutions

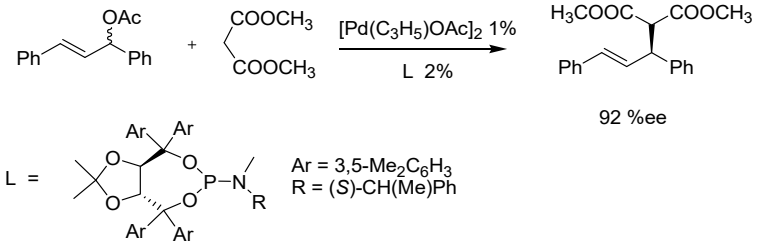
Asymmetric allylic substitution is an important transformation in organic synthesis which in most cases catalyzed by palladium complexes with phosphorus and/or nitrogen ligands.[123] Thus, P,N-TADDOL derived ligands were successfully employed in Pd-catalyzed allylic alkylations of unsymmetrically substituted allyl substrates with

dimethyl malonate. The reactions provided a mixture of the corresponding branched and linear regioisomers in high yields. High enantioselectivities (up to 94 %ee) were obtained for the branched isomers (Scheme 31).[124]



Scheme 31. Allylic substitution catalyzed by a Pd-TADDOL-phosphite-oxazoline complex.[124]

Several examples of monodentate phosphoramidite and phosphite ligands derived from TADDOL have been applied to the asymmetric allylic substitution and provided from good to excellent (up to 92%ee) selectivities (Scheme 32).[125]

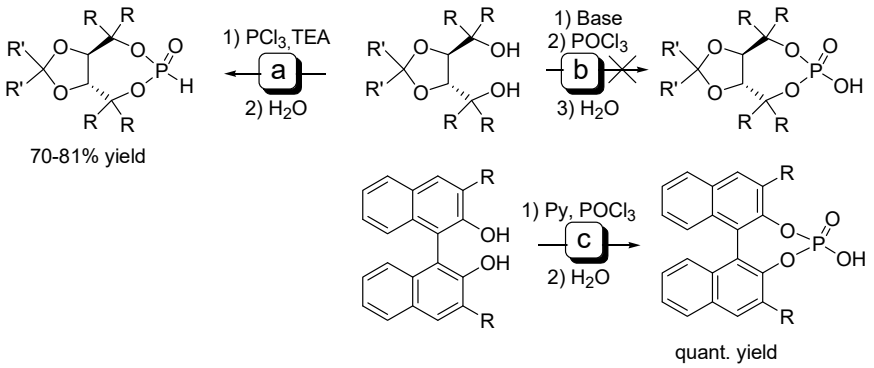


Scheme 32. Allylic substitution catalyzed by a Pd-TADDOL-phosphite-oxazoline complex.[125]

1.2.2 Chiral H-phosphonates and phosphates and their applications in asymmetric synthesis

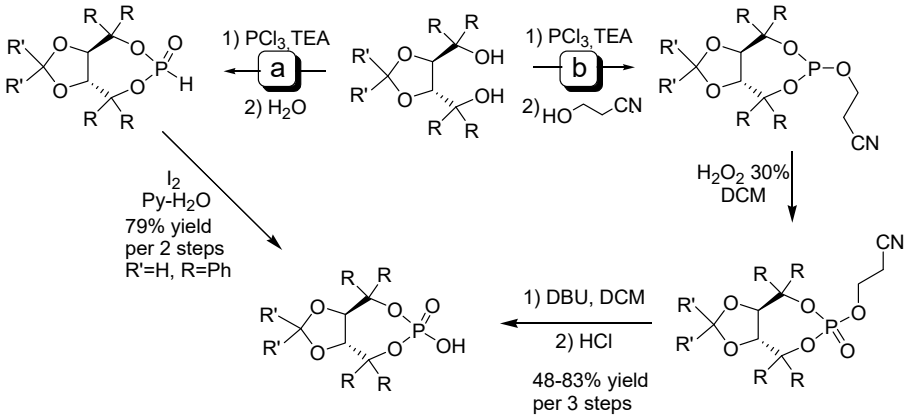
Esters of phosphonic acid, i.e. H-phosphonates, are fairly well described in the literature but their applications in asymmetric synthesis are described only for a limited number of compounds. One of the most described chiral H-phosphonates is based on tetra-aryl substituted TADDOLs[35] However, there are several examples of non TADDOL based chiral H-phosphonates .[126,127]

Most of the H-phosphonates have been prepared from the corresponding diol by reaction with phosphorus trichloride in the presence of a base, followed by hydrolysis (Scheme 33 route **a**).[128–130]



Scheme 33. Preparation of H-phosphonates and phosphates.

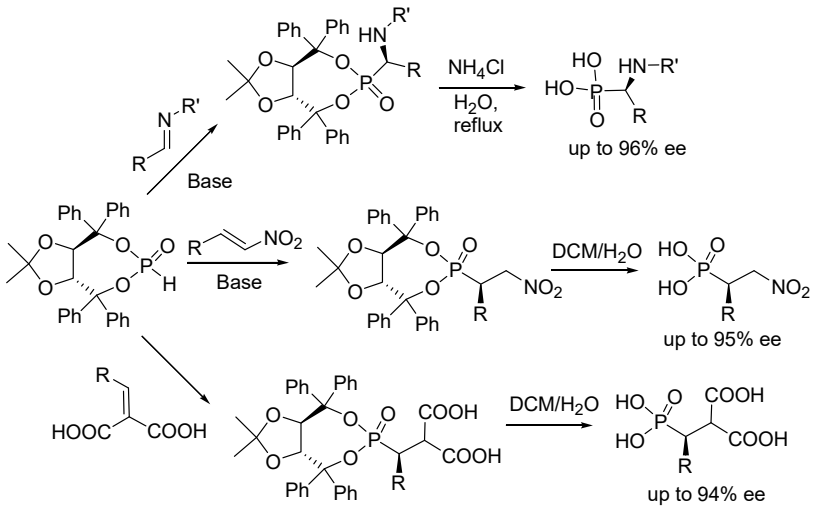
Preparation of TADDOL-based phosphates (phosphoric acids) by reaction of diol with phosphorus oxychloride did not give the desired result (Scheme 33 route **b**), despite that BINOLs showed quantitative yield of the corresponding phosphate (Scheme 33 route **c**).[131]



Scheme 34. Preparation of TADDOL-based phosphoric acids.

TADDOL-based phosphates (phosphoric acids) have been prepared by longer routes, by oxidation of H-phosphonates (Scheme 34), either by direct oxidation (route **a**)[130] or by the oxidation of the triphosphite followed by hydrolysis of the phosphate (route **b**).[102]

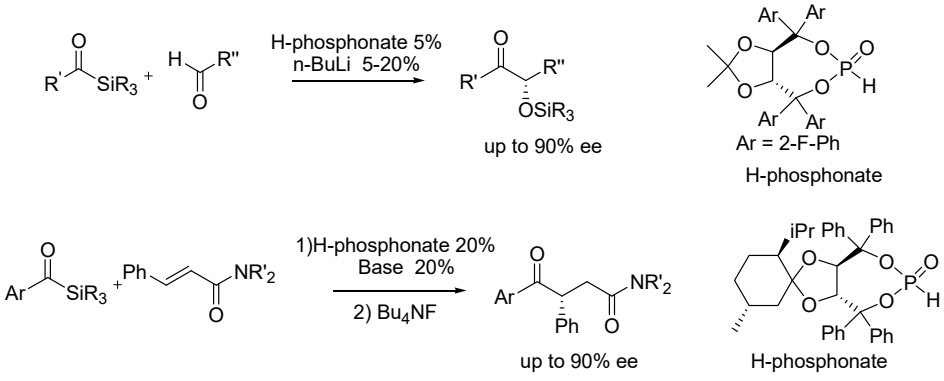
To the best of my knowledge, only few examples of different TADDOL-based-phosphoric acids have been published at the moment.[35,102,130,132,133] This could be a reason of the limited applications of these compounds compared to the BINOL-based phosphoric acids.



Scheme 35. Applications of TADDOL- H-phosphonates as chiral auxiliaries.

Chiral H-phosphonates can, due to the nucleophilic addition of phosphorous, be used as auxiliaries in the asymmetric synthesis. α-Aminophosphonic acids[134–136], precursors to β-aminophosphonic acids[129,137] and other important chiral phosphonic acids [138] have been prepared by this method (Scheme 35).

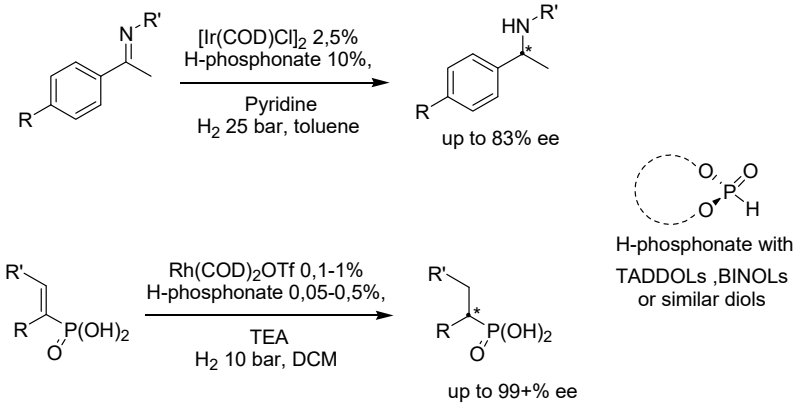
Chiral H-phosphonates have also been used as organocatalysts. The H-phosphonates deprotonated by strong base like butyllithium was shown to catalyze a number of different condensation reactions with different enantioselectivity.[128,139–141] For example, condensation of benzoyl triethylsilane and aldehydes catalyzed by a deprotonated TADDOL H-phosphonate gave up to 90% ee of α-silyloxyketones (Scheme 36).[128] Or condensation of benzoyl triethylsilane with different α,β-unsaturated amides gave chiral γ-diketo-compounds with good to excellent selectivity (Scheme 36).[139,140]



Scheme 36. TADDOL-phosphonate catalyzed asymmetric C-acylations.

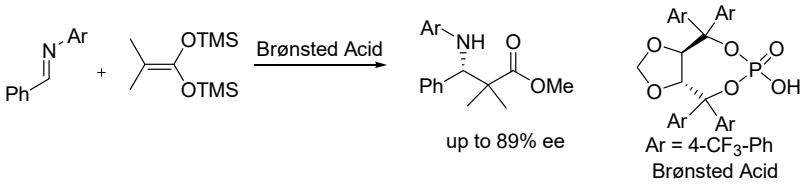
Also, the H-phosphonates have been applied as ligands in Ir catalyzed asymmetric hydrogenations of imines[142] and Rh catalyzed asymmetric hydrogenations of unsaturated phosphonic acids.[143] In both reactions good to excellent selectivities were achieved (Scheme 37).

Chiral phosphates (the esters of phosphoric acid) have been widely used as asymmetric organocatalysts.[144,145] However, only a few TADDOL-based phosphates have been applied as organocatalysts. That is probably caused by the difficulties in preparation of the TADDOL based phosphates described above.



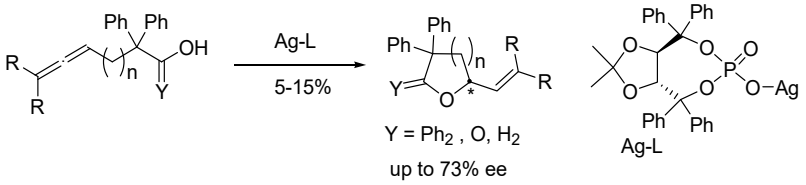
Scheme 37. Transition metal-phosphonate catalyzed asymmetric hydrogenation.

As an example, a highly enantioselective Mannich reaction catalyzed by TADDOL derived chiral phosphates has been reported by Akiyama at al. (Scheme 38).[130]



Scheme 38. Enantioselective Mannich reaction catalyzed by TADDOL-phosphoric acid

Another example is TADDOL-phosphate silver salt catalyzed intramolecular cyclisation of hydroxyl-allenes which gives up to 73% enantiomeric excess (Scheme 39).[133]

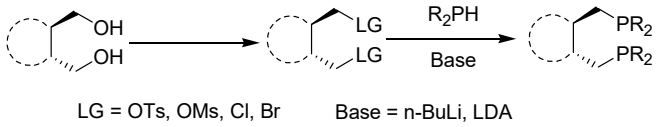


Scheme 39. Enantioselective intramolecular allene cyclization catalyzed by Ag-TADDOL-phosphate.

1.2.3 DIOP and DIOP-like chiral diphosphines and their applications

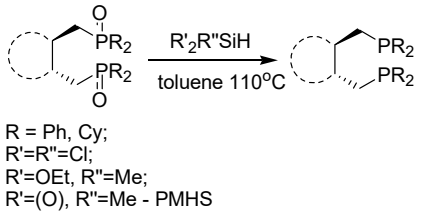
Phosphines are clearly one of the best ligands for different transition metal catalyzed reactions.[146] At the same time chiral diphosphine ligands provide an excellent environment to perform enantioselective catalytic reactions.[147]

(2*R*,3*R*)-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (*R*,*R*-DIOP) was one of the very first chiral ligands used for asymmetric catalysis.[148] It was prepared from the corresponding diols by substitution of hydroxyl groups as described in Scheme 40. Most of chiral DIOP-like diphosphines have been prepared using the same route.[149]



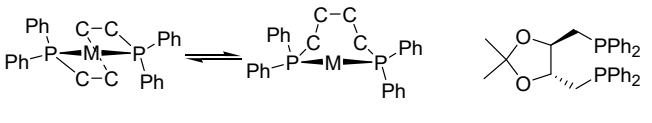
Scheme 40. Preparation of the DIOP-type diphosphines

However, reduction of phosphine oxides has also been used for the preparation of phosphines (Scheme 41).[150–153]



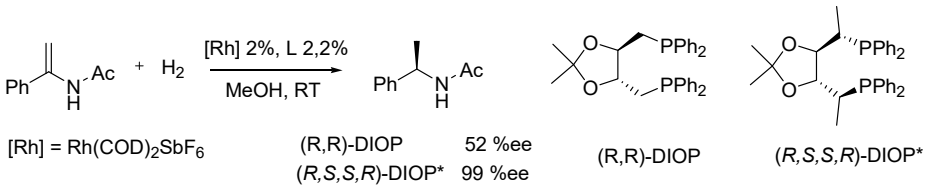
Scheme 41. Reduction of phosphine oxides to phosphines.

DIOP was applied for rhodium-catalyzed hydrogenations of dehydroamino acids and showed moderate enantioselectivities. Tang at al.[154] proposed as a possible reason for the only moderate selectivity. The seven-membered chelate ring of the DIOP metal complex is flexible and cannot have a conformation leading to selectivity (Scheme 42).



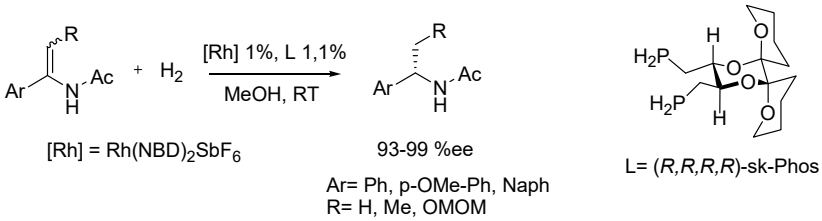
Scheme 42. Explanation of the low efficacy of DIOP ligand from Tang et al.

Indeed introduction of the substituent into CH_2-P arm significantly improves the selectivity of the reaction (Scheme 43).[37]



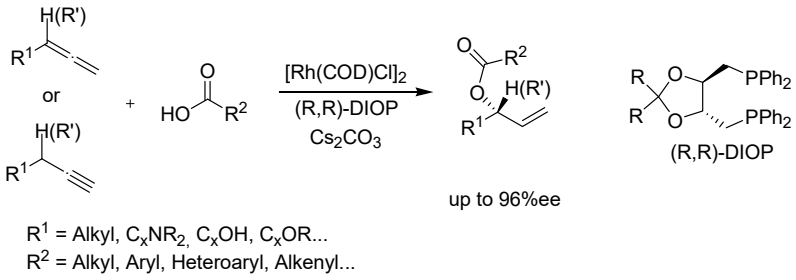
Scheme 43. Significant improvement of selectivity when a methyl group was introduced in the DIOP structure.

Similar diphosphines with a rigid 6-membered ring in their backbone like sk-Phos, provide excellent selectivities in a number of reactions (Scheme 44).[38]



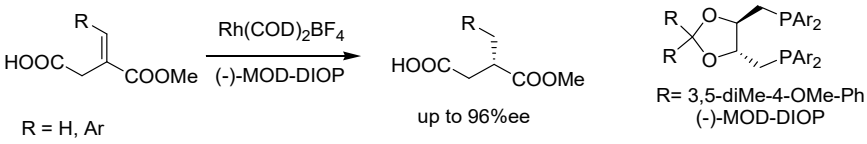
Scheme 44. Highly enantioselective hydrogenation catalyzed by a Rh - sk-Phos complex.

However, applications in which DIOP showed excellent enantioselectivilies were described later (Scheme 45).[155,156]



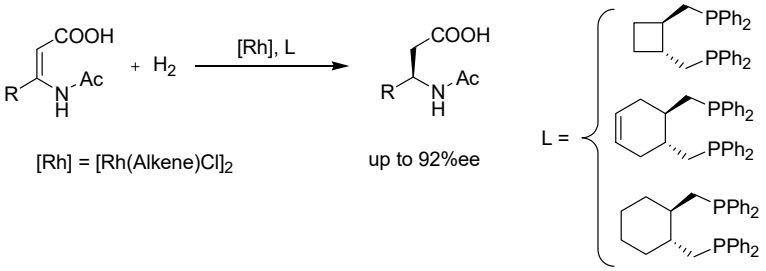
Scheme 45. Highly enantioselective reactions catalyzed by Rh - DIOP complex.

In addition, Achiwa at al. successfully developed MOD-DIOP ligands by varying the diarylphosphine groups. MOD-DIOP was applied in hydrogenation of itaconic acid derivatives and up to 96% ee were obtained (Scheme 46).[157–159]



Scheme 46. Rh-MOD-DIOP catalyzed asymmetric hydrogenation.

A few chiral diphosphines similar to DIOP, but not derived from tartaric acid have been described.[36,160] However, they showed a very good selectivity in several cases (Scheme 47).



Scheme 47. Non-tartaric acid-derived DIOP-like ligands and their application in asymmetric hydrogenation.

To conclude, TADDOLs, DIOPs, their derivatives and similar molecules have over the years showed excellent ability to induce chirality. Many examples have illustrated a great potential of using TADDOL and DIOP like structures in asymmetric catalysis.

2. RESULTS AND DISCUSSION

2.1 Concept of the utilization of the lignan backbone for asymmetric catalysis

Chiral bidentate chelate ligands, such as TADDOLs or BINOLs have, over the years, shown to be excellent molecules for the preparation of various chiral catalysts. The induction of enantioselectivity by TADDOLs and BINOLs is based on the hindrance of the structures containing two adjacent stereocenters, resulting in a fixed angle between the chelating groups. Large substituents shielding one enantioface and *C2*-symmetry of the molecules enhance the efficacy of the enantioinduction.

The lignan hydroxymatairesinol (HMR) has two adjacent stereocenters with similar configurations to TADDOL and, with appropriate modifications, could exhibit similar properties to TADDOL (Figure 5).

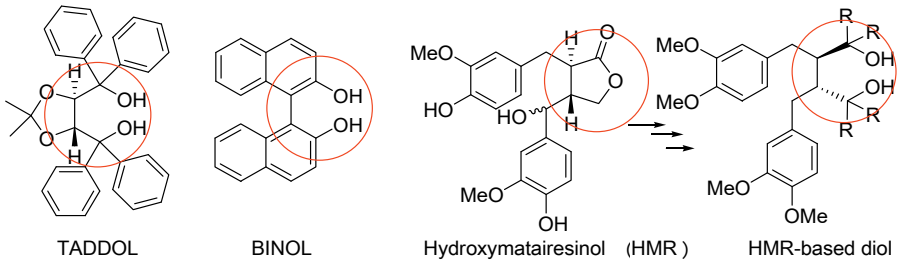


Figure 5. Structural similarities between BINOL, TADDOL and a HMR-based diol.

Furthermore, multiple functionalities make HMR a promising candidate for preparation of tunable chiral catalysts. Tuning of the molecule's geometry is possible either by the variation of the R substituents on the hydroxymethyl chelating arms (Figure 5. HMR-based diol) or by the introduction of different backbones shown in Figure 6. The four proposed types of backbones (Figure 6) should have significantly different properties. The diols based on **type I** backbone (Figure 6) are rigid and nonsymmetrical. **Type III** diol structures are still rigid but already *C2* symmetrical, macrocyclic backbone **type IV** based diols are more flexible and also *C2* symmetrical and the most flexible diols **type II** are still *C2* symmetric (Figure 6).

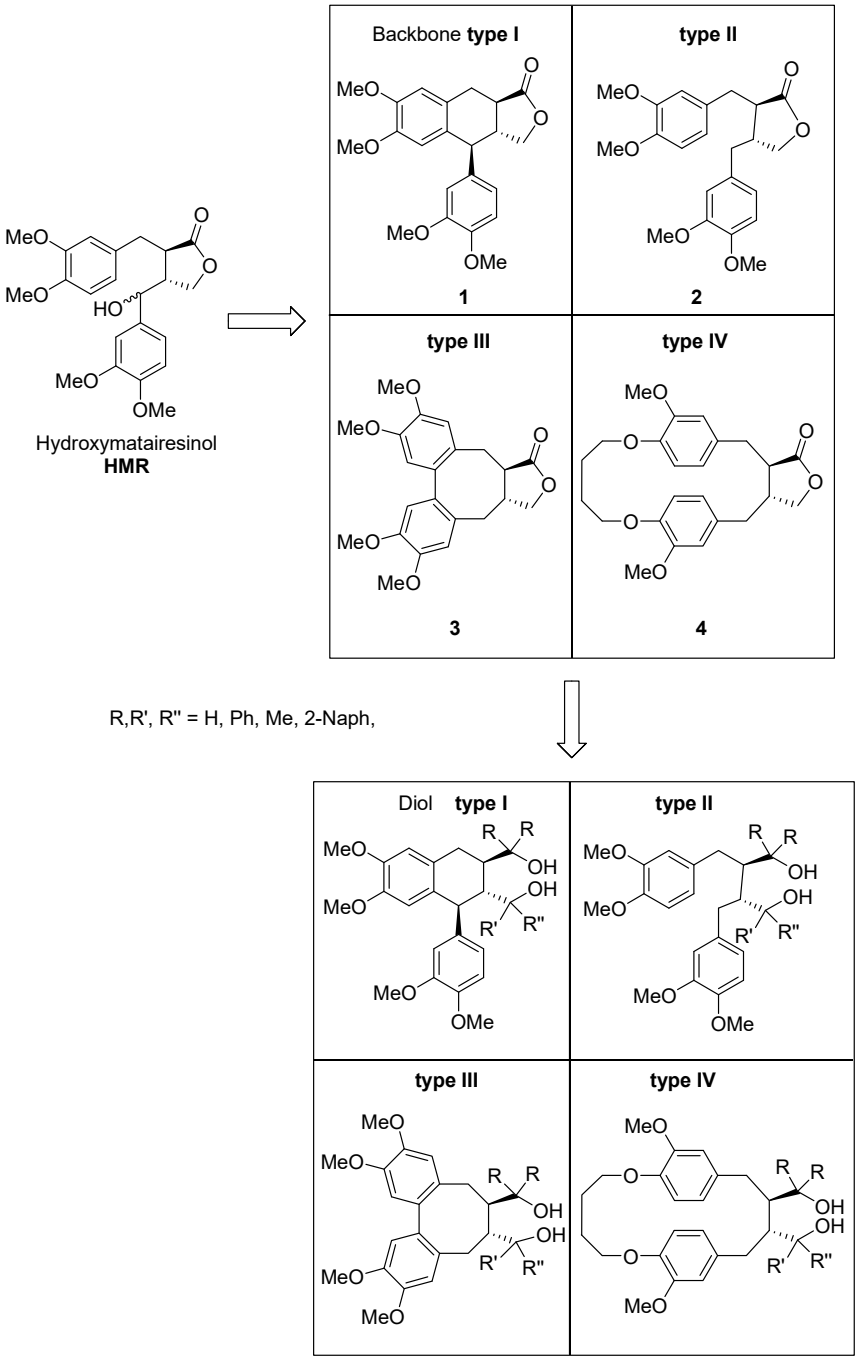


Figure 6. Modification of the hydroxymatairesinol to four types of chiral diols.

These diverse diols could be further used for preparation of chiral phosphines, H-phosphonates, amines, phosphoric acids or other potent ligands for the use in asymmetric catalysis or as organocatalysts.

2.1.1 Molecular modeling

Before performing the synthesis, it was decided to look at the proposed structures by quantum chemical calculation of the minimized energy conformations to compare the geometry of our proposed molecules with the geometry of TADDOL structures. Geometry features for TADDOLs and TADDOL-like structures have been published by Weber at al.[161] and Seebach at al.[47,162] as crystallographic data, NMR structural analysis and as molecular modeling results. From the extensive structure-selectivity studies described in [47] the authors assumed that there is no straightforward dependence of the structure features of the catalyst and selectivity of the diethylzinc addition to benzaldehyde reaction. However, it was shown that some geometry parameters are necessary to form the chelate catalyst, which is crucial for the selective catalytic reaction. In Figure 7 three examples of the most typical TADDOL-like structures with the most critical bond angles in the structures are presented (values for the angles are shown in Table 1.).

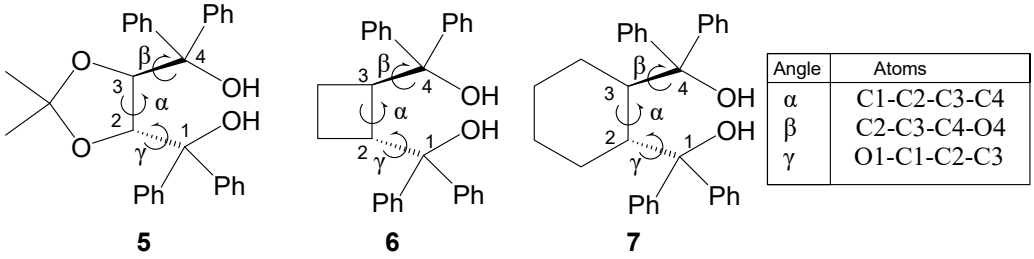


Figure 7. Bond angles for the main types of TADDOL-like structures.

Angles β and γ show the orientation of the diphenylhyroxymethyl arms which is critical for chelating the metal or forming the internal hydrogen bond (both β and γ should be less than 180˚).The 6-membered ring structure **7** has β and γ>180˚, therefore the diphenylhydroxymethyl arms are pointing apart. Rotation of the chelating arms is hindered because of large volume of the phenyl groups therefore Ti-**7** catalyzed diethylzinc addition to benzaldehyde showed no significant selectivity (ee < 20%).[47] Formation of the selective transition state is shown in Figure 8 to illustrate the mechanism of the enantioinduction. This transition state was first proposed by Seebach et al.[47] for the Ti-TADDOLate catalyzed diethylzinc addition to benzaldehyde. Later similar transition state was proposed by Rawal et al.[70] for TADDOL-acid catalyzed aldol reactions.

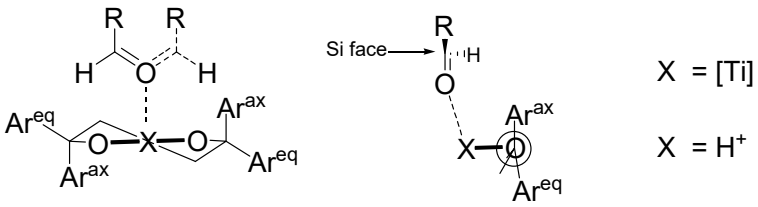
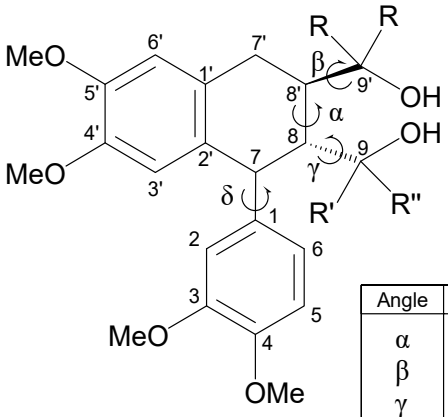


Figure 8. Structure of the transition state, which explains the enantioinduction in TADDOL-catalyzed reactions (proposed by Seebach et al.[47] for Ti-TADDOLate catalyzed diethylzinc addition to benzaldehyde reaction or by Rawal et al.[70] for TADDOL-acid catalyzed aldol reactions.).

It is interesting to notice that the TADDOL-like catalysts with best selectivity had α angle between 265-275˚.[1,47,70,162]

Conidendrin based diols of type I were chosen as substrate for molecular modeling (Figure 9). The numbering of the molecule presented in Figure 9 is based on the lignan nomenclature and will be used herein for all lignan derivatives. The following chiral 1,4-diols were investigated, including the entropy contributions: diphenyl **8** (R=Ph, R'=R''=H), two diastereomers of triphenyl **(9*R*)-9** and **(9*S*)-9** (R=Ph, R'=Ph, R''=H), tetraphenyl **10** (R=R'=R''=Ph), and tetramethyl 1,4-diol **11** (R= R'=R''=Me).



Angle	Atoms
α	C9-C8-C8'-C9'
β	C8-C8'-C9'-O9'
γ	O9-C9-C8-C8'
δ	C2-C1-C7-C2'

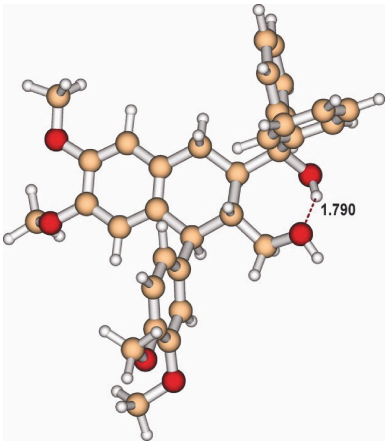
Figure 9. General structure of the modeled diols. R=Ph, Me. R'=H, Ph, Me. R''=H, Ph, Me.

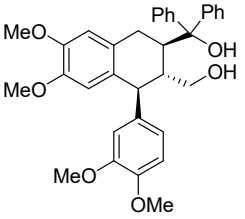
To find the minimum energy of the structures initial torsional analyses were performed for each of the chiral diols on the three single bonds (β−δ) shown in Figure 9 using a step size of 60˚ at molecular mechanics (MM) level as described in our publication.[163] The energetically most favorable structures were optimized with the program GAMESS by using the Hartree-Fock theory. This resulted in a few conformers, which were

reoptimized for the vibrational analysis using the TURBOMOLE program and density functional theory (DFT). Entropy contributions were calculated at 25˚C.

Computational modeling of diphenyl-diol **8** resulted in several minimal energy conformers with minimal differences in geometry (Figure 10). The structure was not proven to be hindered due to the absence of bulky substituents or π–π interactions.

α-Torsional angle of **8** was in the range of 300˚-314˚, while corresponding angle in TADDOLs varied a few degrees around 270˚. At the same time, the distance between diol oxygens was 2.65 Å and therefore suitable for formation of hydrogen bonding or for chelating a metal, which is crucial for the catalytic functionality.

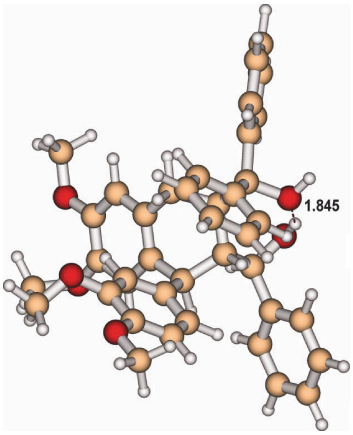


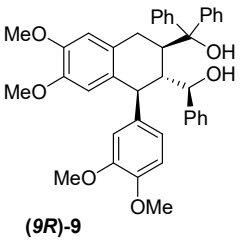


α	311°
β	65°
γ	74°
δ	298°

Figure 10. The most stable conformer of diphenyl 1,4-diol **8.**

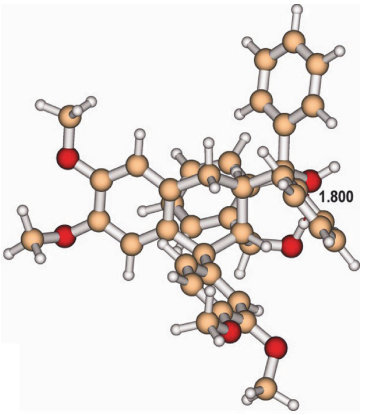
Triphenyl diols **(*9R*)-9** and **(*9S*)-9** seemed more sterically hindered. This was mainly due to the formation of π –π interactions between the phenyl ring at C7 and one of the phenyl rings at C9', as can be seen in Figure 11. The torsional angles changed a lot during the DFT optimizations due to the formation of π –π binding. Thus, the most stable **(*9R*)-9** conformers had torsion angle α between 240° and 270° and conformers of **(*9S*)-9** were closer to 240°. Most triphenyl conformers had the OH groups pointing to the same direction, and could therefore possibly work as catalysts.

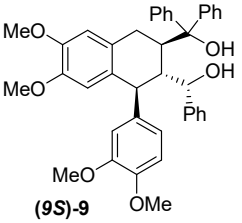




(*9R*)-9

α	257°
β	49°
γ	35°
δ	349°



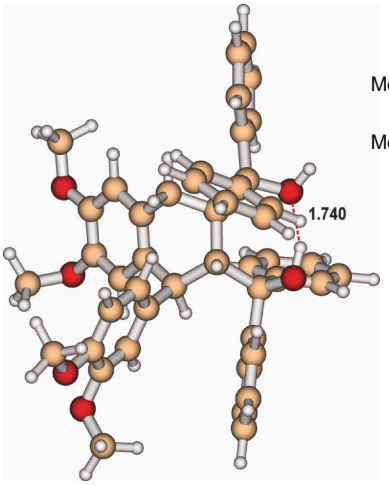


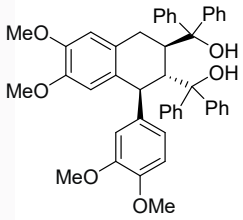
(*9S*)-9

α	268°
β	57°
γ	85°
δ	171°

Figure 11. The most stable conformers of triphenyl 1,4-diols **(*9R*)-9** and **(*9S*)-9** isomers

The target molecule of the series was the tetraphenyl-diol **10**. The structure was significantly sterically hindered. The most stable conformer is shown in Figure 12. Most of the conformers chosen by MM differed a lot when they were optimized by HF, but the DFT optimized structures remained almost identical to the HF optimized ones. Most of the low energy conformers have angle α close to 280° and OH groups pointing to the same direction. However, there are two conformers with the angle α close to 240°, which would give the perfect boat conformation of the aliphatic six-membered ring, and by that a more stable structure. Although these conformers do not have the OH groups pointing to the same direction.



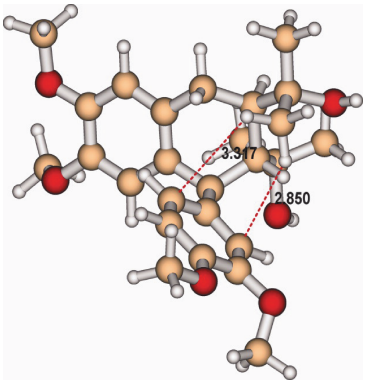


α	283°
β	63°
γ	77°
δ	84°

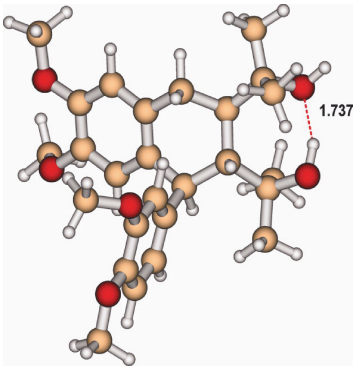
Figure 12. The most stable conformer of tetraphenyl 1,4-diol **10**

Optimization of the tetramethyl 1,4-diol **11** structure resulted in 2 types of conformers A and B (Figure 13) with the minimal difference in energy (by DFT). Conformer A had torsion angle α around 246˚ and the OH groups pointing to different directions. Conformer B had α around 295˚ and the OH groups pointing to the same direction. The difference in energy was up to 12 kJ/mol appeared to be not very significant at room temperature.

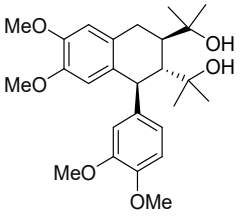
Conformer A



Conformer B



α	246°
β	297
γ	50°
δ	168°



α	295°
β	82°
γ	39°
δ	108°

Figure 13. The most stable conformers A and B of tetramethyl 1,4-diol **11**.

Table 1. Comparison of angles calculated for **8**, **9**, **10** and **11** with corresponding angles of the TADDOL-like structures **5, 6, 7.**

Angle	**5**	**6**	**7**	**8**	**(9*R*)-9**	**(9*S*)-9**	**10**	**11**	
								Conformer A	**Conformer B**
α	267	264	217	311	257	268	283	246	295
β	71	67	297	65	49	57	63	297	82
γ	62	63	297	74	35	85	77	50	39
δ	-	-	-	298	349	171	84	168	108

To conclude, the molecular modeling showed that these sterically hindered 1,4-diols derived from the lignan conidendrin could potentially work as catalysts similar to TADDOLs. In order to test this hypothesis, we continued the work by preparing these compounds starting with the optically pure lignan conidendrin. The other types of the structure were not studied with molecular modeling in this work.

2.2 Synthesis and application of chiral diols derived from lignan hydroxymatairesinool

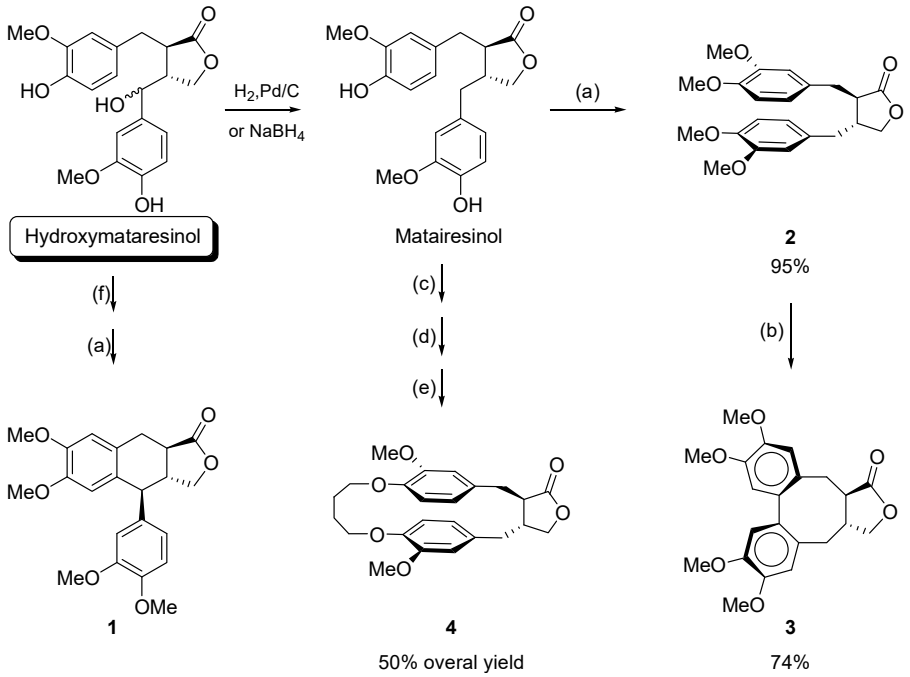
As it has been stated above the aim of this work was 1) to develop diverse methods to derivatize the lignan skeleton (except the lactone function) starting from the natural lignan hydroxymatairesinol and then 2) to convert the prepared lactones to tetrasubstituted structures similar to TADDOL.

To perform the first part of the task we selected four backbones derived from HMR: conidendrin (**1**) is a rigid unsymmetrical structure with one additional stereocenter, 8-membered ring structure (**3**) is also rigid, but possesses different geometry, dimethylmatairesinol (**2**) – fully flexible structure and the macrocycle (**4**) which has a less flexible structure (Figure 6).

The four types of lactones were prepared from hydroxymatairesinol by the following modifications:

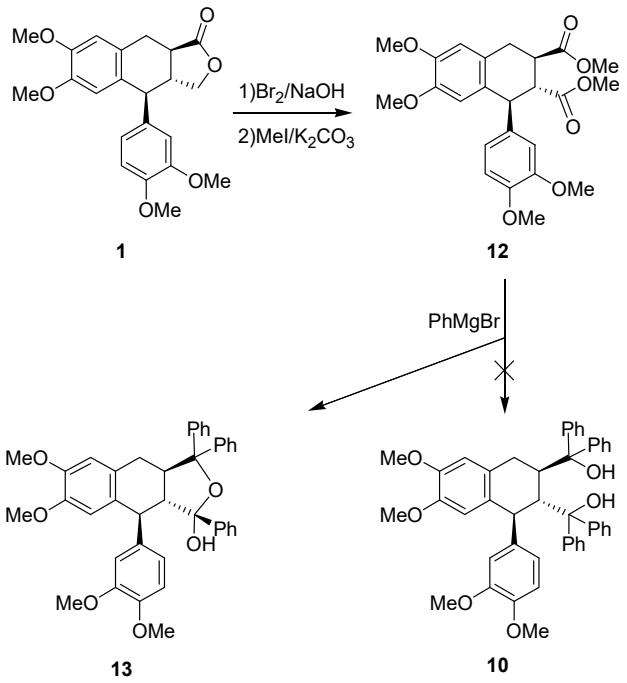
For preparation of the dimethyl-conidendrin structure (**1**) the HMR containing the spruce knot extract was treated with formic acid, then the reaction mixture was crystalized from ethanol and then the phenolic hydroxyls were methylated by methyliodide.[164]

For preparation of the other lactones hydroxymatairesinol was converted to matairesinol by catalytic hydrogenolysis on Pd on carbon.[165] Compound **2** was prepared with quantitative yield from matairesinol by methylation with methyl iodide. Compound **3** was prepared from **2** by intramolecular oxidative coupling with good yield by vanadium (V) oxofluoride.[166] For preparation of macrocyclic compound **4** phenolic groups in matairesinol were allylated followed by cyclisation by methathesis and reduction of the double bond (Scheme 48).[167]



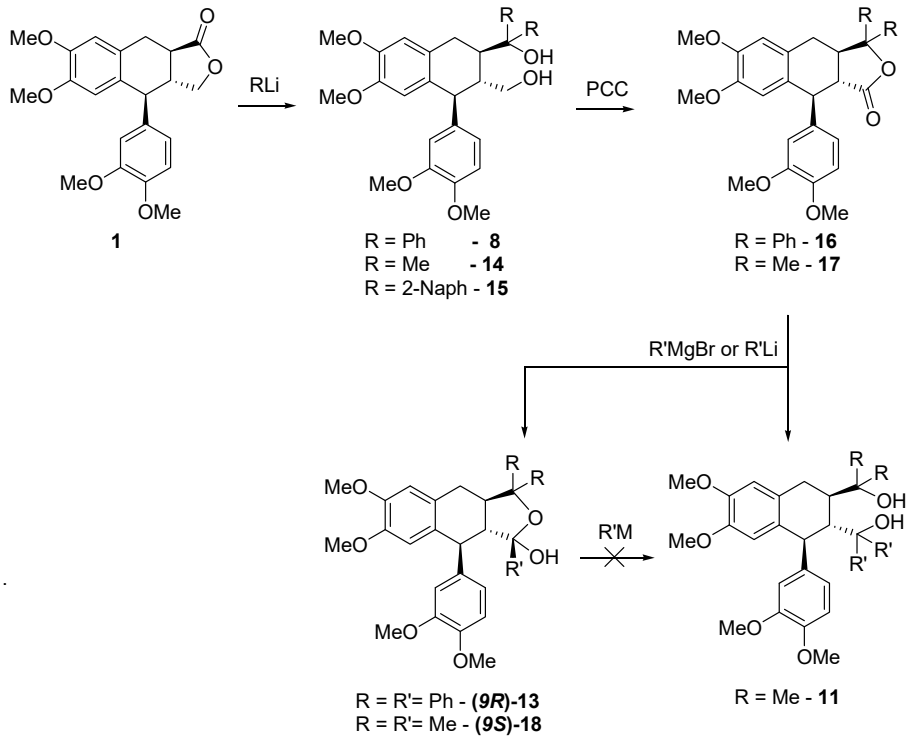
Scheme 48. Synthesis of lactones with different backbones. a) MeI, K_2CO_3, DMF, rt 3h; b) VOF_3, TFA/DCM, -45°C; c) Allyl bromide, K_2CO_3, DMF, rt; d) Grubbs I generation 5%, DCM, rt; e) 5% Pd/C, MeOH, rt. , f)HCOOH, rt.

Only a few methods for the synthesis of TADDOL-like structures have been described in the literature. Usually, the synthesis is based upon the one-pot addition of four alkyl or aryl groups with an appropriate Grignard reagent to the diester of a 1,4-dicarboxylic acid. To evaluate this methodology on the conidendrin structure (**1**), we prepared the diester **12.** However, the Grignard reaction of the diester with excess of phenylmagnesium bromide produced only the undesired hemiketal (**13**) (Scheme 49). This problem has not been previously reported for TADDOLs or similar structures, although the reported yield of the target diol in most cases seldom exceeded 50%.[47]



Scheme 49. The diester synthetic route applied on dimethylconidendrin.

To try an alternative method, stepwise addition reactions and oxidation (Scheme 50) were performed. In this study the arylation and alkylation with the organolithium reagents worked better than the corresponding Grignard reagents. In the reactions of **1** with phenylmagnesium bromide, the yields of **8**, were usually around 65%, and with phenyllithium, yields of 85% or higher were obtained.



Scheme 50. Stepwise synthesis of the diols.

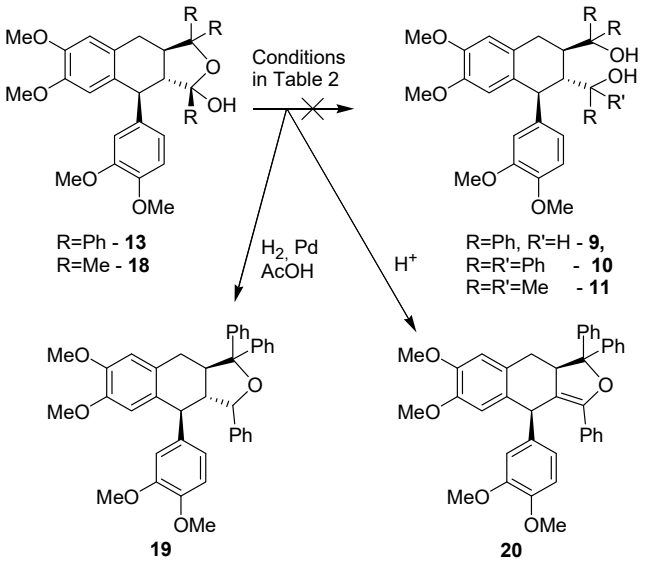
The oxidation of the primary alcohol (**8**, **14**) with pyridinium chlorochromate (PCC) proceeded smoothly as a stepwise process. In reactions performed with 1 eqv. PCC the hemiacetal was the major product and could be isolated in 60% yield. This hemiacetal was shown to be very stable and the corresponding aldehyde could not be detected by NMR in aqueous solutions of the hemiacetal. When excess of PCC was used the oxidation gave excellent yields (~90%) of the lactone (**16**, **17**).

Phenylation of 9',9'-diphenyl-dimethylretrodendrin (**16**) with either phenylmagnesium bromide or with phenyllithium gave only the hemiketal **(*9R*)-13** as the major product and about 15% of the other diastereomer.

The stereochemical configurations of the hemiketals were determined by NMR and assigned as 8*R*,8'*R*,7*S*,9*R* for (***9R*)-13** and 8*R*,8'*R*,7*S*,9*S* for (***9S*)-13**. No signals from the corresponding ketone or the tetrasubstituted diol could be detected in the NMR spectra. To explain this phenomena methylation and phenylation of 9',9'-dimethyl-dimethylretrodendrin (**17**) and methylation of 9',9'-diphenyl-dimethylretrodendrin (**16**) were performed. Only the methylation of 9',9'-dimethyl-dimethylretrodendrin (**17**) gave a mixture of the target 9,9,9',9'-tetramethyl-dimethylcyclolariciresinol (**11**) and the trimethyl-hemiketal (**18**). The formed mixture had a constant ratio of **11** and **18**

(1:1.3) and only one diastereomer of the hemiketal was formed. According to these results, we assumed that in this reaction the 9'9'-disubstituted lactone structure (**16**, **17**) formed one diastereomer of the hemiketal, which is extremely stable and there is no equilibrium between this hemiketal and the ketone. The other hemiketal seemed to react further to give the diol product **11**.

To study the possibility to further react the intermediate hemiketals (**13, 18**) to the diols, the hemiketals were isolated and treated in different nucleophilic and reductive conditions. However, in most cases, only the starting material was isolated and no desired reactivity was observed (Scheme 51, Table 2).



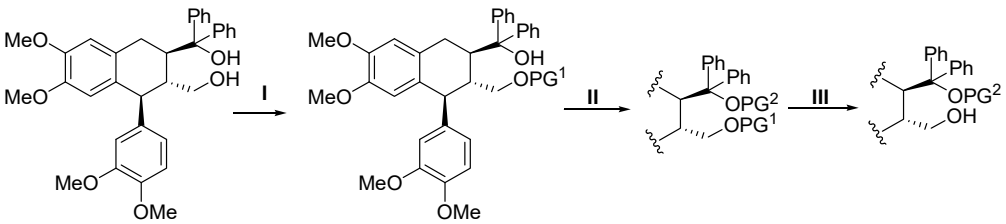
Scheme 51. Attempts to open the hemiketals **13** and **18**.

Table 2. Attempts to open the hemiketals **13** and **18**.

R	*R'*	*Conditions*	Result
Ph	Ph	PhMgBr, THF, RT to reflux	No reaction
		PhLi, THF, -78°C to RT	No reaction
		PhLi, TMEDA, THF, -78°C to RT	No reaction
		PhLi, 12-crown-4, THF, -78°C to RT	No reaction
Ph	H	$LiAlH_4$, THF, RT to reflux	No reaction
		$NaBH_4$, MeOH/H_2O	No reaction
		$Zn(BH_4)_2$, THF	No reaction
		H_2 5bar, Pd/C, MeOH, 60°C, 24h	No reaction
		H_2 5bar, Pd/C, AcOH, 60°C, 4h	THF-structure (**19**) formed
		HCl (pH~1), THF/H_2O, RT, 2h	DHF-structure (**20**) formed
		AcOH, 70°C, 15h	DHF-structure (**20**) formed
Me	Me	MeMgBr, THF, RT to reflux	No reaction
		MeLi, THF, -78°C to RT	No reaction
Me	H	$LiAlH_4$, THF, RT to reflux	No reaction

Computational analysis of the hemiketal **18**[164] supported the fact that the thermodynamically favoured isomer should be **(*9S*)-18** (the Gibbs energy of the stable hemiketal isomer was lower by 24–28 kJ/mol compared to the other diastereomer)**.** The atomic charges showed that the reactivity of **(*9S*)-18** should be also lower. However, a complete explanation for the lack of equilibrium with the corresponding ketone and the extremely poor reactivity of the hemiketals would require additional studies.

To overcome the problem of the extreme stability of the hemiketals, we investigated the strategy where no ring can be formed during the oxidation i.e. protection of the tertiary OH-group (**PG^2**, Scheme 52). We therefore set out to selectively protect the primary alcohol (**PG^1**) followed by the protection of the tertiary alcohol and then deprotection of **PG^1** (Scheme 52). A number of different protective groups and conditions were tested (Table 3)**.** Different groups as **PG^1** were successfully introduced but only the methyl group could be introduced as a **PG^2** (Scheme 52).



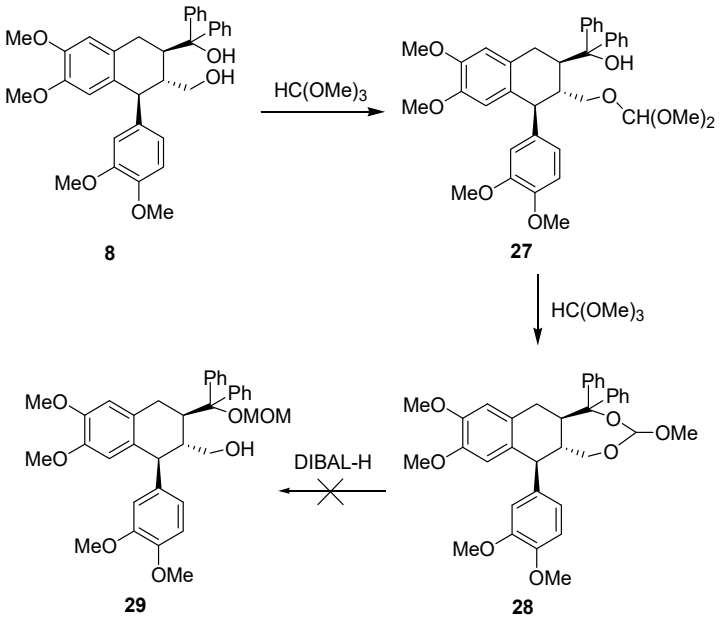
Scheme 52. Attempts to protect the more hindered OH-group.

Table 3. Reaction conditions in the attempts to protect the more hindered OH-group

PG[1]	*Conditions I*	*Yield of **PG[1]** protected product*	*PG[2]*	*Conditions II*	Results
TMS	TMSCl, TEA, DCM,	**22**, 68%	Bn	NaH, DMF then BnBr	No reaction
Bn	NaH, DMF then BnBr	**21**, 90%	TMS	NaH, DMF then TMSCl	No reaction
			THP	DHP, TsOH, DCM	No reaction
			MOM	MOM-Cl, TEA, DCM	No reaction
				MOM-Cl, Py, DMAP, DCM	No reaction
				MOM-Cl, DMAP in Pyridine	No reaction
				NaH, DMF then MOM-Cl	No reaction
				BuLi, THF, -78ºC then MOM-Cl	No reaction
				MOM-OMe/P_2O_5	No reaction
			Ac	NaH, DMF then AcCl	No reaction
			Me	BuLi, THF then MeI	**25**, 90% yield
TBDMS	TBDMSCl, TEA, DCM,	**23**, 85%	Bn	NaH, DMF then BnBr	TBDMS was substituted by Bn, **21**, 45% yield
$H(MeO)_2C$-	$(MeO)_3CH$, RT, 18h	**27**, 75%	(MeO)CH	$(MeO)_3CH$, reflux 120h	**28**, 44% yield
Allyl	NaH, DMF then Allyl-Br	**24**, 79%	MOM	BuLi, THF then MOMCl	No reaction

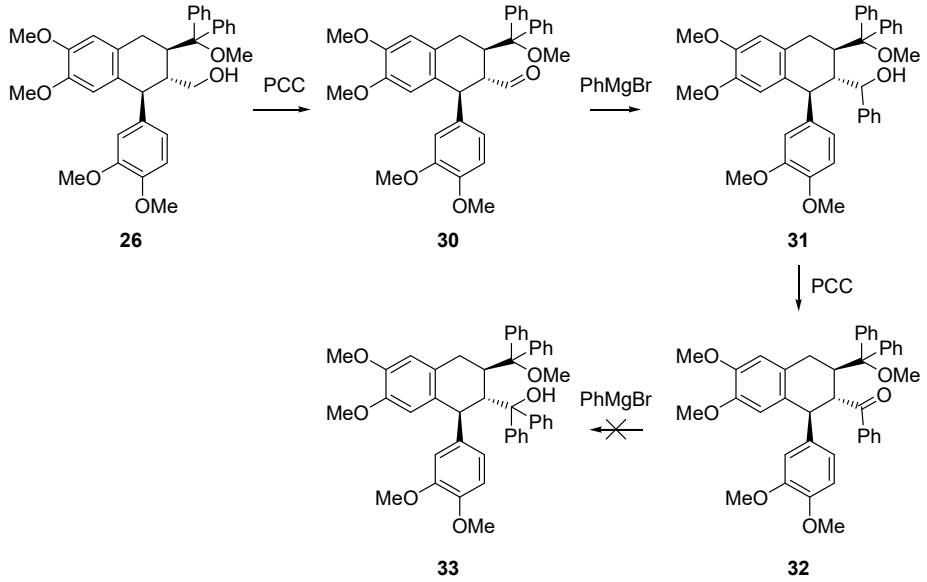
The special route of MOM-protection of one of the OH groups of the diol was also tested (Scheme 53).[168] However, the cyclic orthoester did not react with DIBAL-H as expected.

Since 9O-benzyl-9'O-methyl-9',9'-diphenyl-dimethyl-cyclolariciresinol (**25**) was obtained the benzyl group was removed by Pd/C catalyzed hydrogenolysis to give alcohol **26** in excellent yield (95%).



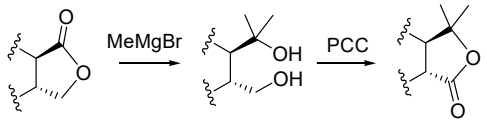
Scheme 53. The „orthoester" route to protect the more hindered OH-group.

Then the free hydroxymethyl group of **26** was oxidized to the aldehyde (**30**), phenylated to **31** and oxidized again to give the ketone **32** (Scheme 53). However, it turned out that this ketone didn't react with phenylmagnesium bromide or with phenyllithium. This suggested that the desired tetraphenyl structure (**33**) was too sterically hindered to be prepared by the described routes (Scheme 54).



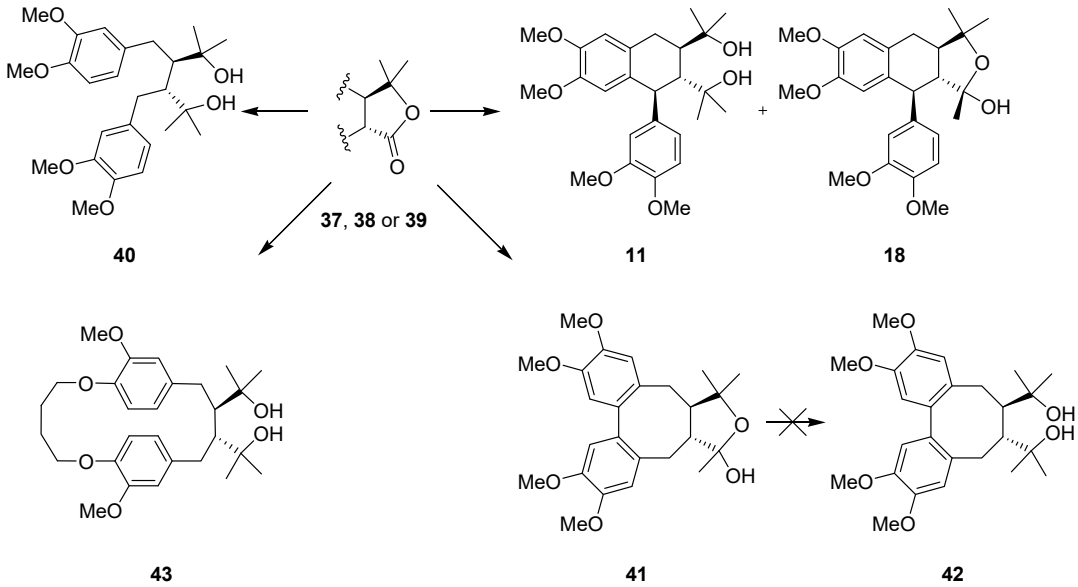
Scheme 54. Attempt to prepare the tetraphenyl substituted diol from the methyl protected compound **26**.

Since it turned out that the tetraphenyl derivatives were not possible to be prepared by this synthetic route, we made an attempt to prepare the tetramethyl-derivatives of different lignan structures. For this purpose the lactones **2**-**4** were methylated with methylmagnesium bromide with excellent yield. The prepared diols were oxidized with pyridinium chlorochromate to give the appropriate dimethyl-lactones with good to excellent yields (Scheme 55).



Scheme 55. Preparation of the dimethyl-lactones. For the full structures, see Appendix 1.

Then dimethyl-lactones (**37**, **38**, **39**) were methylated with methylmagnesium bromide (Scheme 56). The reaction with lactones **37** and **39** first produced a mixture of diastereomers of hemiketals which in excess of methylmagnesium bromide slowly reacted to give tetramethyl-diols **40** and **43**. In case of lactone **38,** the formed mixture of diastereomers of hemiketals **41** was stable and did not undergo any changes in these reaction conditions.



Scheme 56. Reaction of dimethyl-lactones with methylmagnesium bromide. For the full structures, see Appendix 1.

The macrocyclic tetrametyl-diol **43** was crystallized from benzene to give crystals which were used for x-ray analysis. The x-ray result is shown in Figure 14. It is interesting to notice that the structure is not symmetric which makes it possible to solve enantiomers in the x-ray. The reason of the asymmetry of the molecule is a hydrogen bonding between the diol hydroxyls. It is so significant that it distorts the parallelism of the benzene rings at 15°. Despite this fact, the NMR spectra indicates the symmetry of the molecule.

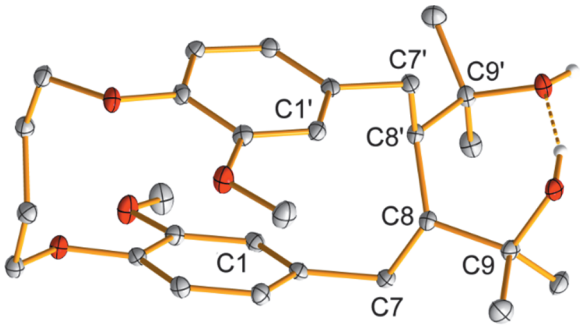
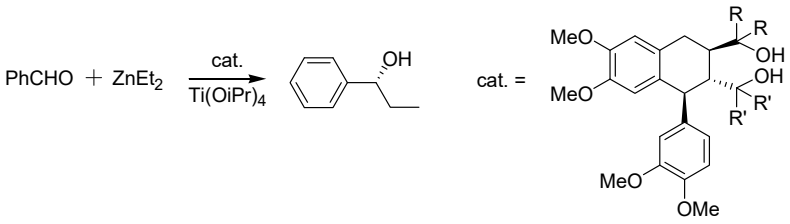


Figure 14. X-ray structure of diol **43**.

Looking at these results, it can be assumed that our more flexible structures also had quite stable 3-substituted hemiketals and the introduction of the forth substituent was slow (up to 48h). In case of lactones **37** and **39**, with excess of methylmagnesium

bromide, we observed the formation of almost 50:50 mixture of hemiketal and tetrametyl-diol in 1h and then a very slow conversion of the hemiketals to tetrametyl-diols (several days). This could be explained by the assumption that the attack of the lactone from one face gave a diastereomer of the hemiketal, which was very stable. The other diastereomer immediately converted to the ketone and reacted with the excess of the Grignard reagent. An example of the reaction of lactone **38** with methylmagnesium bromide is more interesting from this point of view. The only product of the reaction was the hemiketal **41** as a mixture of diastereomers. The mixture was not possible to separate chromatographically, but NMR spectra of the mixture were solved because of significant difference in shifts of all the signals of the diastereomers. So significant difference in NMR indicated the significant difference in conformation of the 8-membered ring (could be a flipping of the ring to the other diastereomer). This turned us to suggest an explanation: the attack of the lactone **38** from one face led to the stable diastereomer on the hemiketal **41**. The attack from the other face led to diastereomer which was not stable and underwent the 8-memberd ring's flipping which resulted in another stable diastereomer of the hemiketal.

To evaluate these novel 1,4-diol structures the well-known TADDOL catalyzed diethylzinc addition to benzaldehyde was employed as a testing reaction.



Scheme 57. Diethylzinc addition to benzaldehyde (Test reaction)

Table 4. Diethylzinc addition to benzaldehyde

cat	*R*	*R'*	*Cat. loading, %*	*Conversion, %*	**ee, %**
8	Ph	H	10	95	5(*R*)
			20	100	5(*R*)
14	Me	H	15	97	3(*R*)
11	Me	Me	15	95	20(*R*)
			20	100	20(*R*)
44	H	H	15	98	0
15	2-Naphthyl	H	15	100	2(*R*)

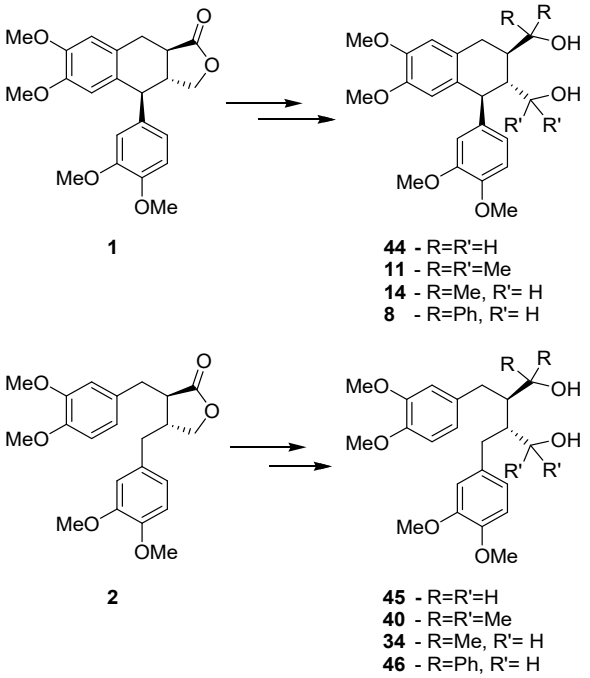
However the diol **11** showed a reverse selectivity in comparison to the corresponding (-)-*R,R*-TADDOL (Scheme 57, Table 4). The major isomer in the reaction catalyzed by our diols was shown to be *R* in contrast to the *S*-isomer formed in the (-)-TADDOL-catalyzed reaction.[169]

Despite the fact that the selectivity was only moderate, for example: ~20% ee with **11** as a catalyst, the observed phenomena is of considerable interest.

2.3 Chiral H-phosphonates and phosphates derived from the lignan backbone

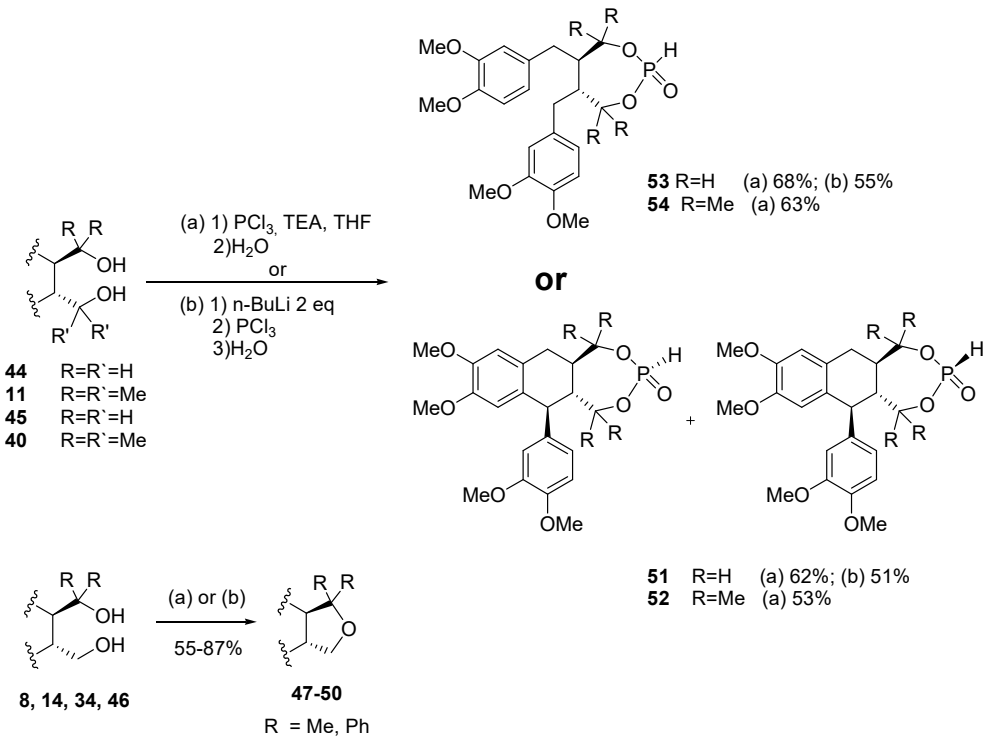
Since a series of chiral 1,4-diols derived from natural lignan hydroxymatairesinol had been prepared, we were looking for different applications for the diols in the field of asymmetric catalysis. H-phosphonates and phosphates are frequently used in this field (see introduction). So, it was decided to prepare some of this phosphorous compounds from the diols. For this purpose, several diols derived from lignans matairesinol and conidendrin were selected.

The lactones **1** and **2** (Scheme 58) were either reduced by $LiAlH_4$ to the corresponding unsubstituted diols (**44** and **45**)[170] or alkylated to the other diols as described above.



Scheme 58. Preparation of the diols

The diols were then used as starting materials for the syntheses of chiral H-phosphonates (Scheme 59). By using a procedure (a) developed for TADDOL derivatives,[35] a series of reactions of diols with phosphorus trichloride in presence of excess of triethylamine as a base were performed, followed by the hydrolysis to H-phosphonates. As a result we observed the formation of desired products only when unsubstituted or tetramethyl substituted derivatives were used. In the case of unsymmetrically substituted derivatives (**8**, **14**, **34** and **46**) the formed products were predominantly a result of intramolecular etherification (products **47**-**50**) (Scheme 59.).



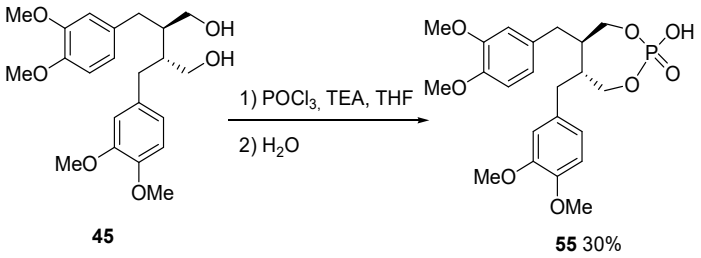
Scheme 59. Reaction of the diols with phosphorus trichloride. For the full structures, see Appendix 1.

When the diols were deprotonated with butyllithium to dialcoholates and then treated with phosphorus thrichloride followed by hydrolysis to the H-phosphonate (procedure (b)) the same result was obtained. Nevertheless, the yield of the desire H-phosphonates using the procedure (a) was slightly higher in a number of cases. The more simple experimental conditions of method (a) makes this method the preferable choice.

The C_2 symmetrical diols **45** and **40** gave the phosphonates **53** and **54** as a single diastereomer. In contrast, phosphonates **51** and **52**, prepared from diols **44** and **11** with C_1 symmetry, were obtained as mixtures of diastereomers.

To investigate the possibility to form other phosphoric esters we performed the reaction of the diol **45** with phosphorus oxychloride in presence of excess triethylamine followed by hydrolysis to phosphoric acid ester **55** (Scheme 60). The phosphate **55** was obtained in moderate yield (30%). The other diols **44**, **40** and **11** under the same conditions led to complex mixtures of products.

The alternative way to produce the phosphoric acid by oxidation of the H-phosphonate by iodine described by Akiyama at al.[171] was also examined. The oxidation of the H-phosphonates **53** and **54** in wet pyridine[172] led to hydrolysis of the product resulting with the starting diols **45** and **40**, respectively.



45 **55** 30%

Scheme 60. Reaction of the diol 20b with phosphorus oxychloride.

Unlike the C_2 symmetrical **45** and **40**, H-phosphonates **53** and **54** and phosphate **55** showed complete asymmetry of the molecules. For example, the ^{1}H-NMR spectra showed a difference of 0.12 ppm in chemical shifts of benzylic protons in **53** (Figure 15). Therefore, introduction of the prochiral phosphorus to the C_2 symmetric molecules created no additional stereocenter but eliminated symmetry which was in the starting molecules.

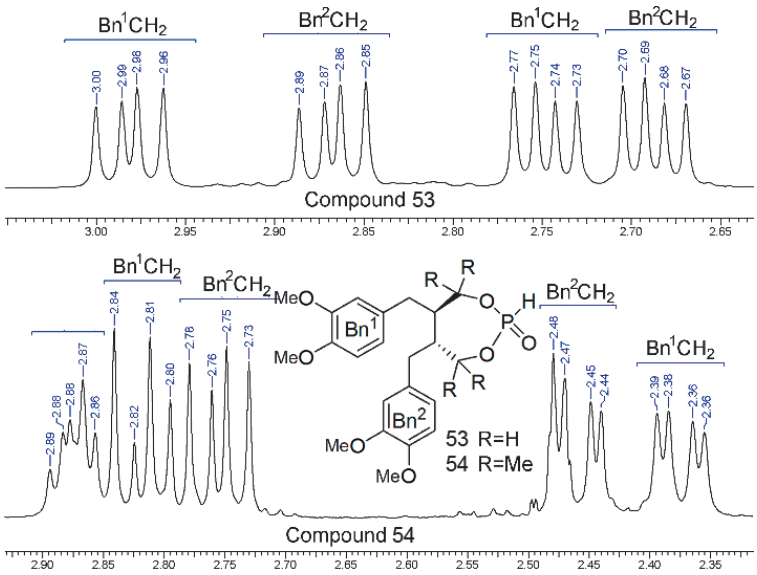


Figure 15. NMR signals of the benzylic protons in compounds **53** and **54**.

Unsubstituted H-phosphonate **51** was obtained as a mixture of diastereomers in the ratio of 1:1, according to ^{31}P-NMR. However, we were able to selectively crystallize one of the diastereomers from benzene which made possible to assign all the signals in the ^{1}H-NMR spectra for both diastereomers, respectively. The tetramethyl-substituted H-phosphonate **52** was obtained in the diastereomeric ratio of 3.5:1 according to ^{1}H and ^{31}P-NMR spectra. A clear difference in chemical shifts of the signals of the diastereomers made it possible to assign all signals of the major isomer and most of the signals of the minor isomer.

^{31}P-NMR shifts for unsubstituted H-phosphonates **51** (11,46 and 11,63 ppm) and **53** (11,60 ppm) were significantly higher than the shifts for tetramethylsubstituted H-phosphonates **52** (-2,18 and -3,23 ppm) and **54** (-2,71 ppm), although P-H coupling constants were close to each other in all presented H-phosphonates (698-707 Hz).

The diastereoselectivity in formation of the tetramethyl-substituted H-phosphonate **52** in contrast to nonselective formation of the unsubstituted H-phosphonate **51** showed significant directing role of the methyl substituents which could be utilized in application of the H-phosphonates in the asymmetric synthesis and catalysis.

To conclude, methods for preparation of H-phosphonates and phosphates from chiral lignan backbones were developed. Four new H-phosphonates and one phosphate were synthesized and characterized. Diastereoselective formations of H-phosphonates from sterically hindered diols were shown. Non-hindered diols showed no selectivity. The

diastereoselective formations of the substituted H-phosphonate is recognized as an indirect sign of the enantioinductive properties of the molecule.

2.4 Lignan backbone-based phosphines. Ligands for asymmetric hydrogenations

Transition metal catalyzed asymmetric hydrogenation is one of the most critical reactions for the field of modern catalysis. This reaction requires a chiral ligand to create the asymmetric environment and to stabilize the metal complex during the reaction. Phosphine ligand has been proven to be the most suitable for this purpose.[147]

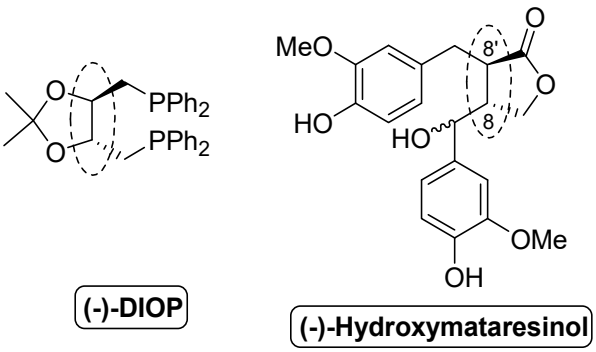
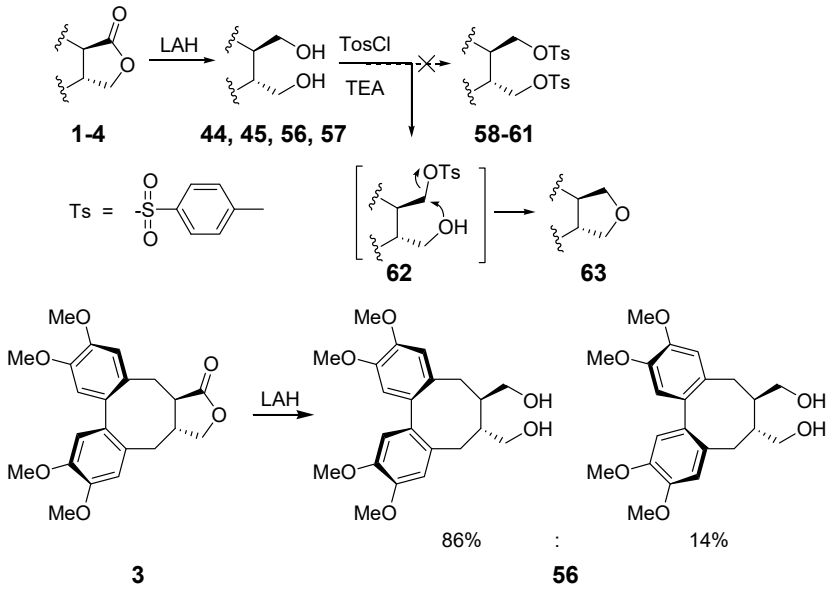


Figure 16. Similarity in stereochemistry for DIOP and Hydroxymatairesinol.

As a continuation of this work the idea of using hydroxymatairesinol for preparation of different chiral diphosphine ligands and their application in asymmetric hydrogenations was explored. The structural similarity of hydroxymatairesinol and DIOP structure is shown in Figure 16.

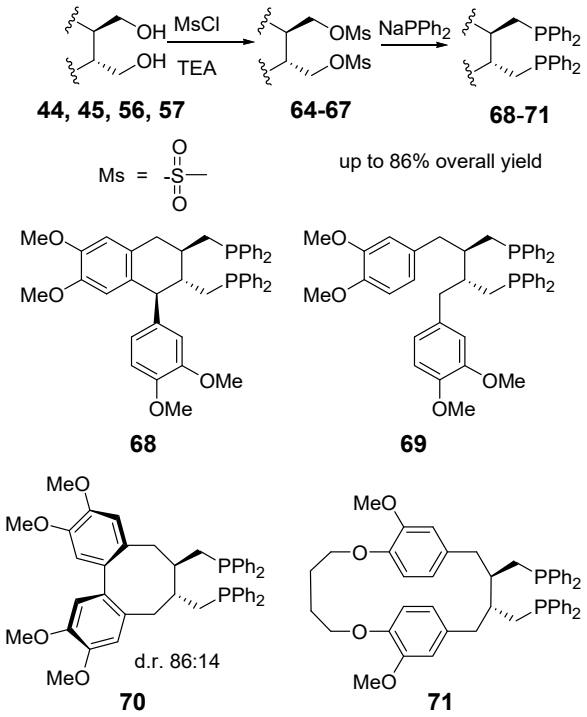
To prepare lignan-derived phosphines, hydroxymatairesinol was transformed into four different lactones (**1**-**4**) as described earlier (Scheme 48). The lactones were then reduced to the chiral diols (**44**, **45**, **56**, and **57**) by lithium aluminum hydride in good yields (Scheme 62, the synthesis has been described already for diols **44** and **45** in Scheme 58. Racemization of the Ar-Ar chiral axis was observed during the reduction of the lactone **3** and diol **56** was obtained as a mixture of diastereomers (86:14) (Scheme 61). The ratio of the isomers did not depend on the temperature of the reaction, and remained constant after 5 h of reflux in toluene. Separation of the diastereomers was not feasible and all subsequent transformations were performed with the mixture of isomers.

To transform the diols to the corresponding phosphines, the common literature procedure via tosylates was investigated.[36] Unfortunately, the only reaction observed was the internal substitution of hydroxyl to give the THF-structure **63** (Scheme 61). One of the reasons for the formation of the product **63** could be bulkiness of the tosyl group. Since the lignan backbone is massive itself, it left no space for the second OTs group and the intermediate **62** underwent internal reaction which led to the product **63** (Scheme 61).



Scheme 61. Attempts to prepare diol-ditosylates. For the full structures, see Appendix 1.

As an alternative, we examined the smaller mesyl group. Dimesylates **64**-**67** were prepared in excellent yields from the diols **44**, **45**, **56**, **57** by treatment with mesyl chloride in presence of excess of triethylamine as a base (Scheme 62). Substitution of the mesylate groups with sodium diphenylphosphide proceeded smoothly to give the desired phosphines in good to excellent yields.



Scheme 62. Preparation of the phosphines. For the full structures, see Appendix 1.

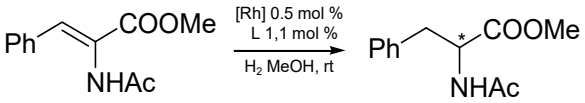
To evaluate these phosphines as ligands for asymmetric catalysis we chose two model prochiral substrates for the rhodium-catalyzed hydrogenation, 2-acetamidocinnamic acid methyl ester (**72**) and 1-acetamidostyrene (**73**).[154,173] 2-acetamidocinnamic acid methyl ester (**72**) was prepared from the commercially available 2-acetamidocinnamic acid by esterification with methanol/thionyl chloride.[174] 1-acetamidostyrene (**73**) was prepared by methylation of the benzonitrile with methylmagnesium bromide and subsequent acylation of the prepared imine salt.[175]

The catalytic reaction was performed at the atmospheric pressure in a flow of hydrogen in contrast to the most of the literature hydrogenation conditions (1.1-50 Bars of H_2, autoclave).[154] The active catalyst was prepared by premixing of the phosphine with dichloro-tetraethylene-dirhodium complex (CAS 12081-16-2). First attempts of the reaction were made with 1% catalyst loading, but later the catalyst loadings were decreased to 0.5% with retention of reproducibility. The conversion was monitored by HPLC or GC, and was over 95% in all reactions. Due to the small scale of the test reactions the isolation of the products was not performed.

The results of the hydrogenations are presented in Tables 4 and 5. As clearly seen from Table 5, the selectivity for substrate **72** was from poor to moderate, which was in good correlation with results for DIOP (ee up to 55%)[148] and for other ligands related to

DIOP.[37,38] Only the nonsymmetrical phosphine **68** (Entry 1) gave moderate selectivity (~40% ee). It should be noted that the selectivity of the reaction, carried out with phosphine **69** as a catalyst was opposite to the reaction catalyzed with phosphines **68**, **70** and **71**. It was speculated that it could be caused by the flexibility of the phosphine **69** which allows the other conformation of the catalytically active species compared to more rigid phosphines **68**, **70** and **71**.

Table 5. Results of the hydrogenation of 2-acetamidocynnamic acid methyl ester



72 **74**

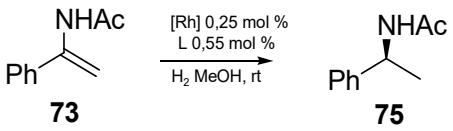
[Rh] = $[RhCl(C_2H_4)_2]_2$

Entry	*L*	*Cat. loading, %*	*ee*, % (config)
1	**68**	1	40 (*S*)
2	**69**	1	8 (*R*)
		0.5	9 (*R*)
3	**70**	1	15 (*S*)
4	**71**	1	25 (*S*)

For substrate **73** the reaction was more selective (Table 6). Good selectivity (75-84 % *ee*) was observed for all C_2-symmetric phosphines (**69**-**71**), while the nonsymmetric phosphine **68** gave only moderate selectivity (62% *ee*). These results were also in a good agreement with the results for DIOP-type or similar ligands. DIOP* and sk-Phos giving excellent selectivities with the substrate **73**, while with substrate **70** the selectivity was only moderate.[37,38]

It was interesting to notice that the best selectivity (84% *ee*) was obtained using the diastereomeric mixture of phosphine **70**. This could possibly be explained by the fact that the minor diastereomer is catalytically inactive.

Table 6. Results of the hydrogenation of 1-acetamidostyrene



73 **75**

[Rh] = $[RhCl(C_2H_4)_2]_2$

Entry	*L*	*Cat. loading, %*	*ee*, % (config)
1	**68**	0.5	62 (*S*)
2	**69**	0.5	75 (*S*)
3	**70**	0.5	84 (*S*)
4	**71**	0.5	81 (*S*)

Despite the fact that no excellent selectivities were obtained with the described phosphines, further investigations should be performed. Most likely, these phosphines could show much better enantioselectivities with the other substrates.

Therefore, the concept of producing phosphines from naturally occurring chiral lignans and their utilization in asymmetric catalysis has a great potential.

3. CONCLUDING DISCUSSION

3.1 Summary

The concept of utilizing the lignan backbone for preparation of asymmetric catalysts was proposed and supported with the in-silico conformational analysis. Further, the synthetic routes for preparation of series of sterically hindered chiral diols were developed.

Unfortunately, the most hindered diols were not possible to prepare by tested methods because of the unexpected problem, outstanding stability of several hemiketals – 3-substituted lactols, which was not previously described in the literature. The problem was studied in details, but no methods to overcome the problem were found. Some of the prepared diols were utilized in asymmetric catalysis and demonstrated up to moderate enantioinduction.

Also, a few chiral H-phosphonates and phosphates were prepared using the diols as starting materials. Potential enantioinductive properties of the structures were indirectly indicated.

The diols were also used for preparation of the series of chiral phosphines which were applied as ligands in rhodium catalyzed asymmetric hydrogenation and showed moderate to high enantioselectivities.

3.2 Conclusions and future perspectives

This work showed that HMR from Norway spruce could work as a good starting material for the preparation of various types of asymmetric catalysts.

Despite the fact that the proposed tetraphenyl diols were not possible to prepare, some of the prepared diols showed moderate ability of enantioenduction in model reactions. It would be good to examine the diols on other substrates or even other catalytic reactions since the diols could show a much higher selectivity in other model reactions.

Several extremely stable hemiketals were prepared in attempts to produce tetrasubstituted diols. The hemiketals were investigated in details. However, the phenomenon of the stability of the hemiketals and their synthetic modification could be explored further.

Some chiral diols derived from hydroxymatairesinol were converted to H-phosphonates and phosphate. The H-phosphonates were not examined for the induction of enantioselectivity in this study. This should be performed in our laboratory in the nearest future. A few conditions for oxidation of H-phosphonates to phosphates should be also examined. The method of direct phosphate preparation, starting from diol and phosphorus oxychloride, should be optimized.

The possibility of using the prepared phosphate as asymmetric catalysts was described. However, the sterical hindrance of the catalyst was probably not enough to significantly induce the enantioselectivity. Alternative routes to more sterically hindered phosphates could still be explored.

The prepared H-phosphonates were not examined for the induction of enantioselectivity. However, they could be utilized as chiral auxiliaries, as asymmetric organocatalysts (in presence of a strong base) and as ligands for the asymmetric organometallic catalysis. These applications should be examined for the H-phosphonates in the nearest future.

Four phosphines which were prepared starting from the diols were applied for rhodium catalyzed asymmetric hydrogenation reactions. In one reaction the phosphines showed low to moderate enantioselectivity. At the same time, in another reaction all the phosphines showed good selectivity. Therefore, the catalytic reaction should be still optimized to get higher enantioselectivities. The phosphine moiety could be also changed and optimized, i.e. diphenylphosphine could be substituted by dicyclohexylphosphine or by ditertbutylphosphine.

Overall, the lignan backbone showed very high potential to be used for preparation of the asymmetric catalyst. However, the area needs to be further explored.

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5. Appendix 1. List of Substances

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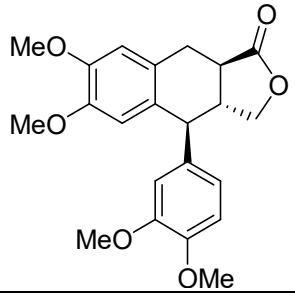
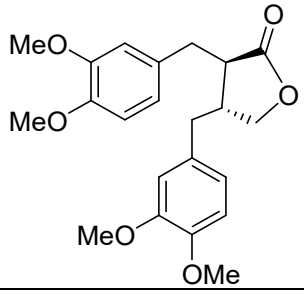
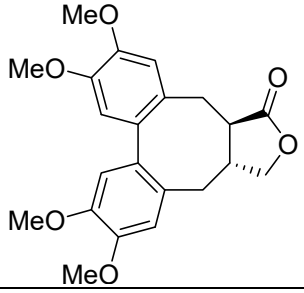
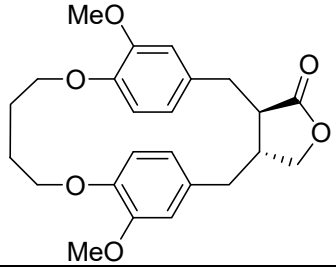
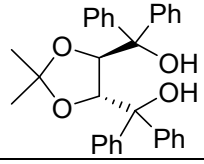
1	
2	
3	
4	
5	

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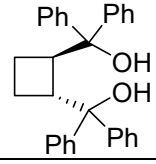
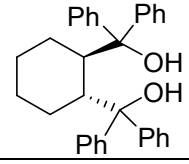
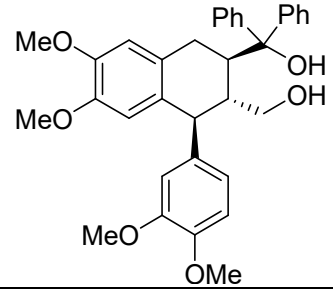
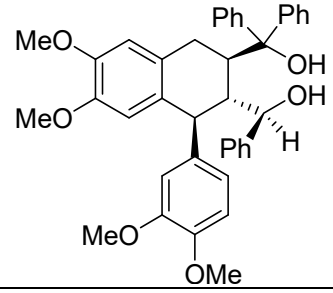
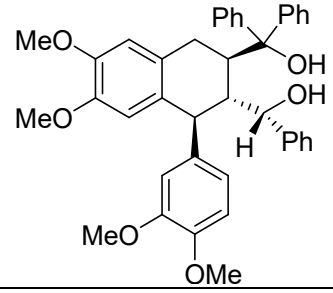
6	
7	
8	
(*9R*)-9	
(*9S*)-9	

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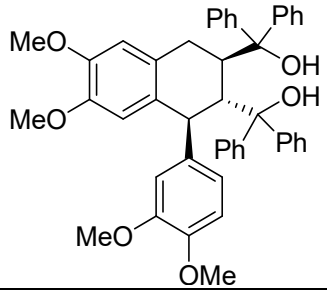
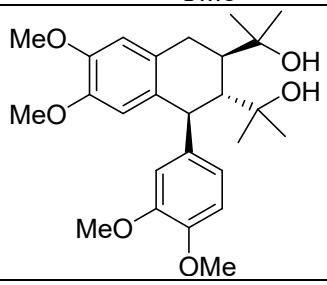
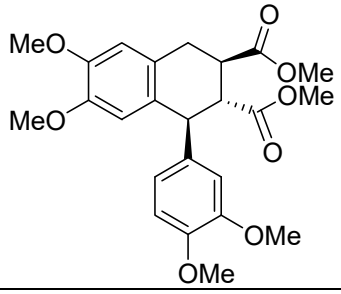
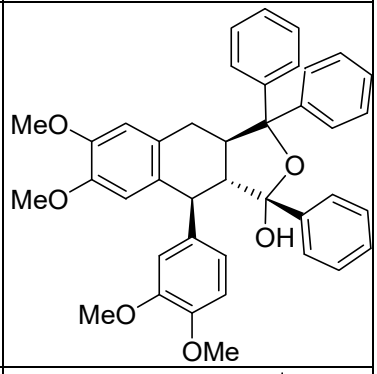
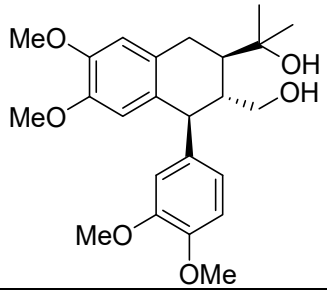
10	
11	
12	
13	
14	

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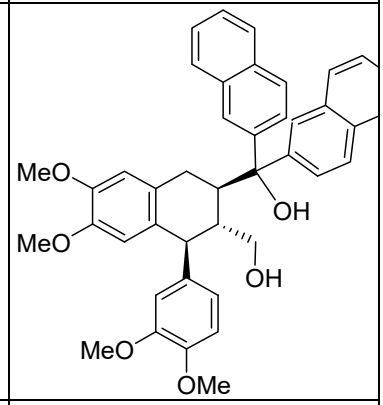
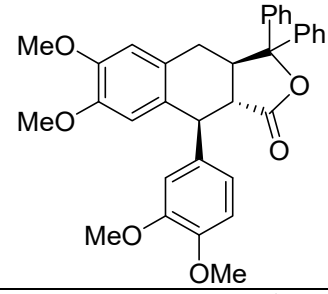
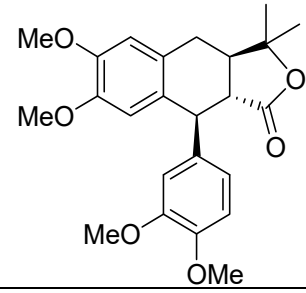
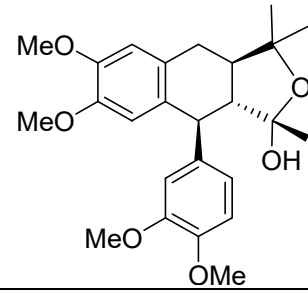
15	
16	
17	
18	

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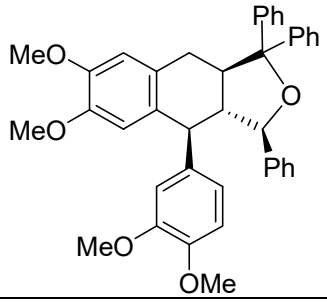
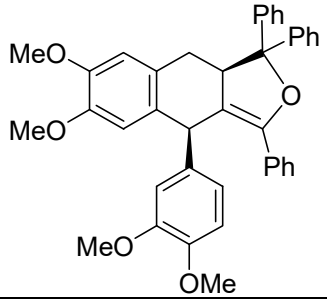
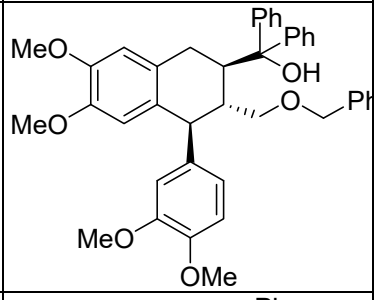
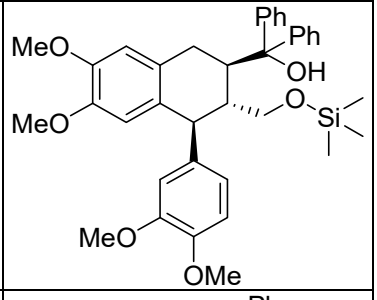
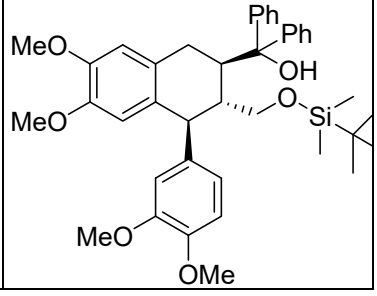
19	
20	
21	
22	
23	

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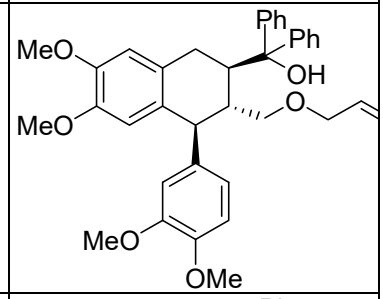
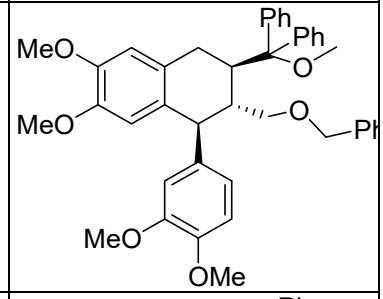
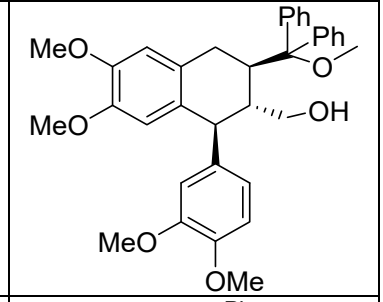
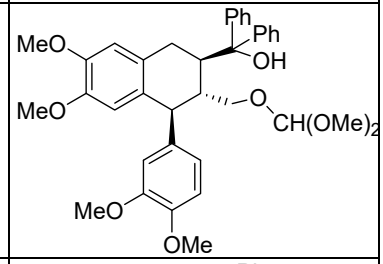
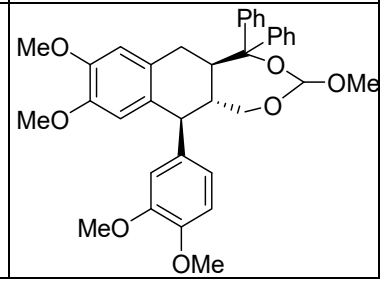
24	
25	
26	
27	
28	

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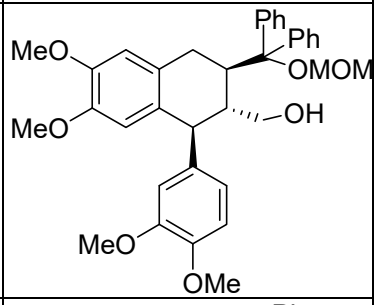
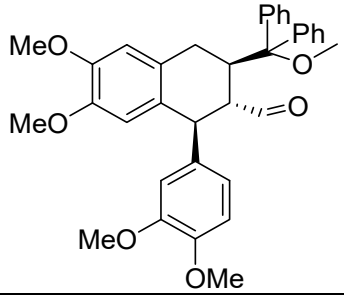
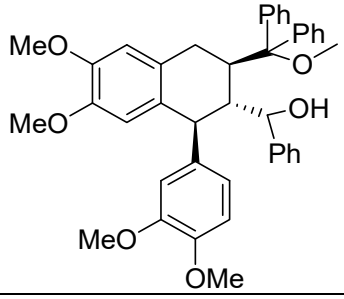
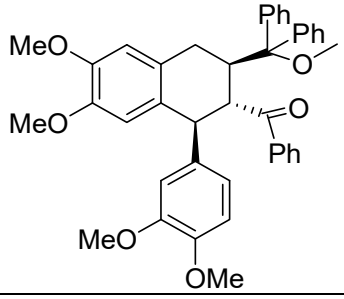
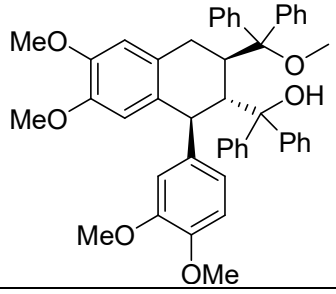
29	
30	
31	
32	
33	

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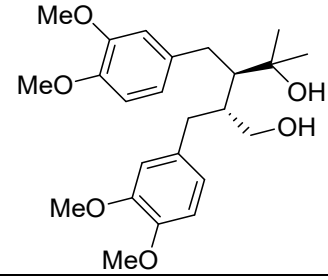
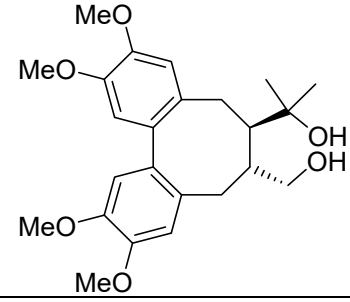
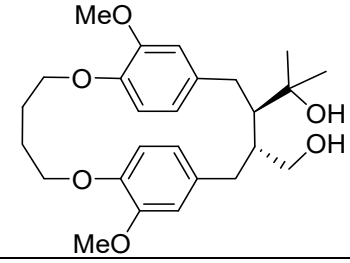
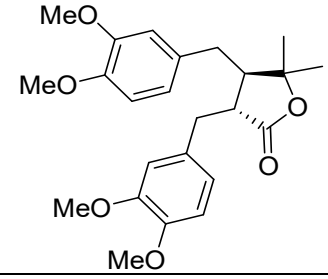
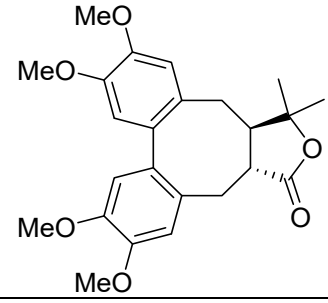
34	
35	
36	
37	
38	

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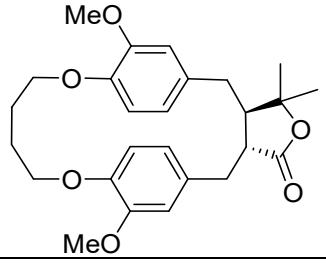
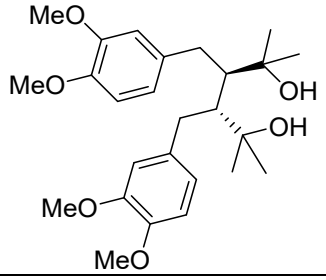
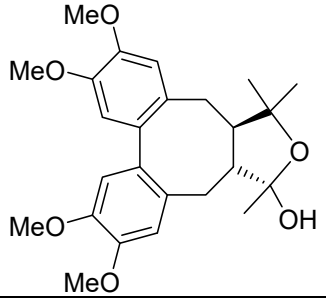
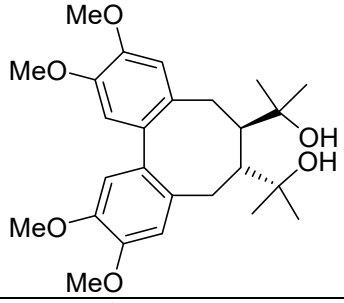
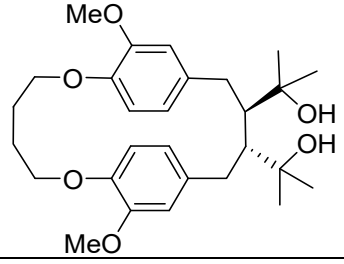
39	
40	
41	
42	
43	

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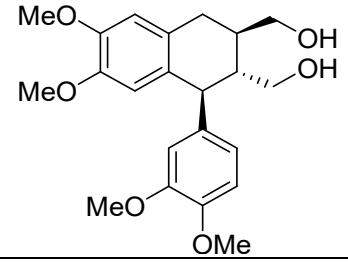
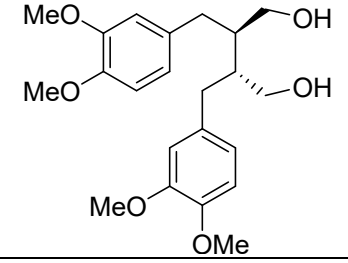
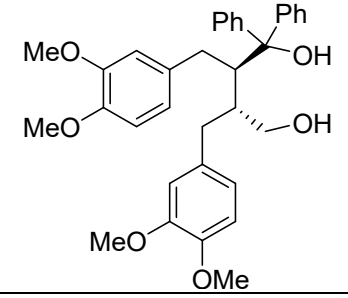
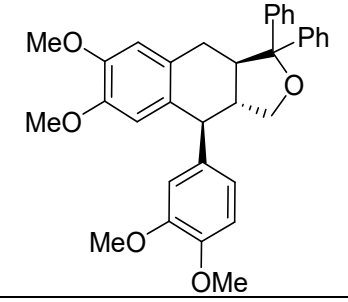
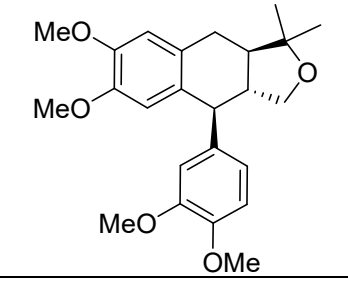
44	
45	
46	
47	
48	

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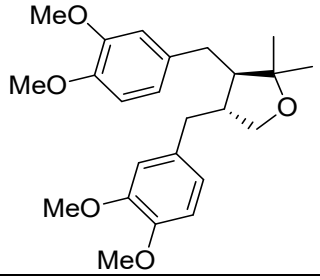
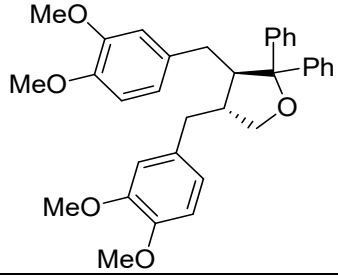
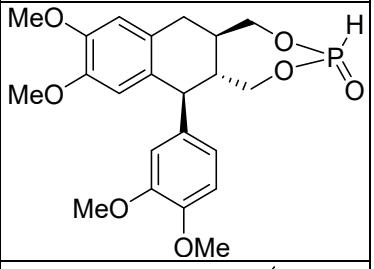
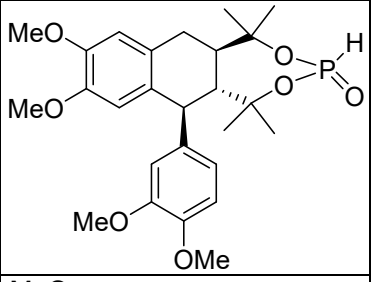
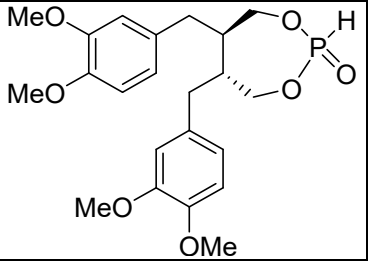
49	
50	
51	
52	
53	

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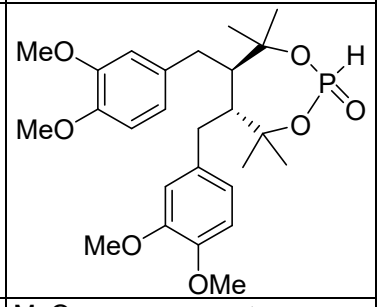
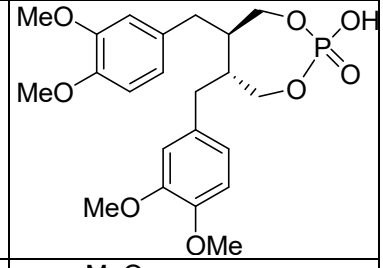
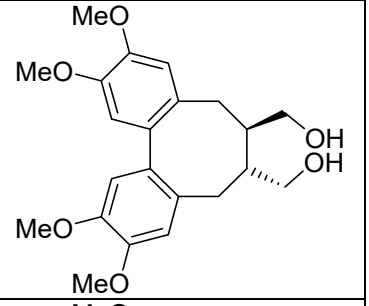
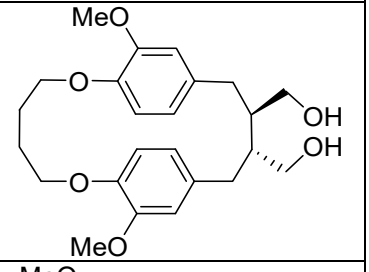
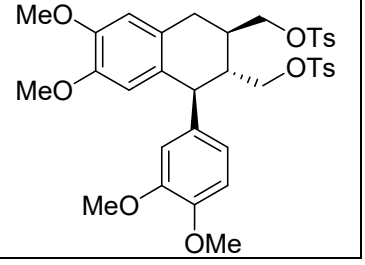
54	
55	
56	
57	
58	

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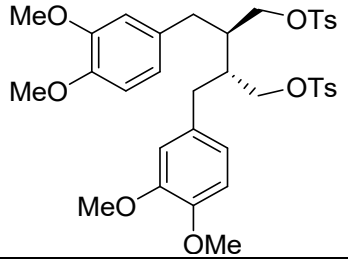
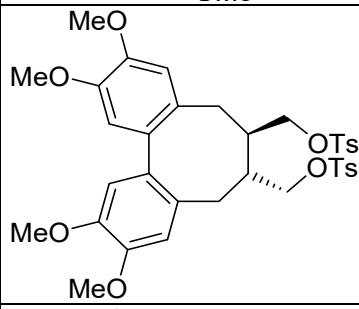
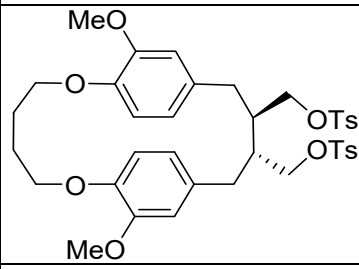
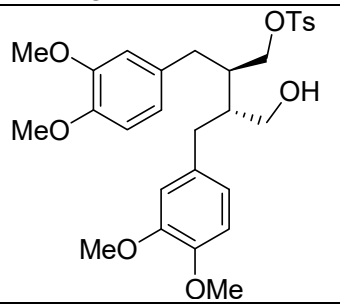
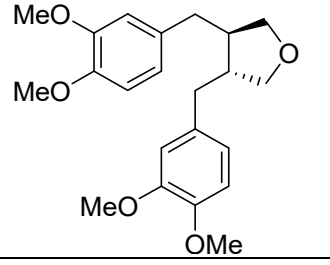
59	
60	
61	
62	
63	

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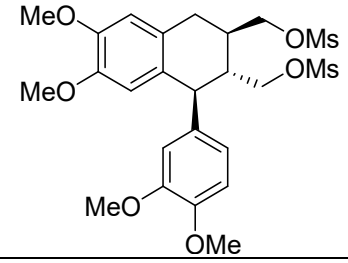
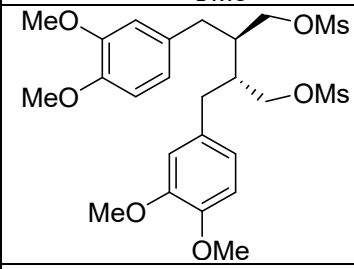
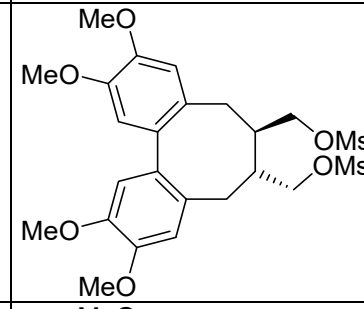
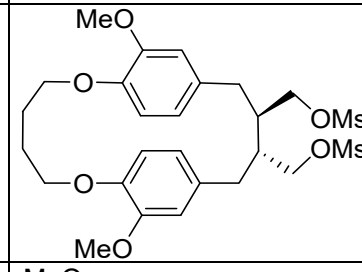
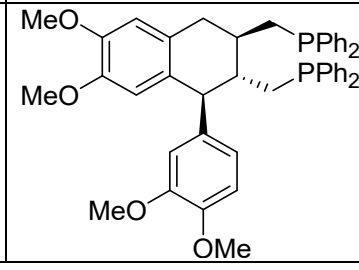
64	
65	
66	
67	
68	

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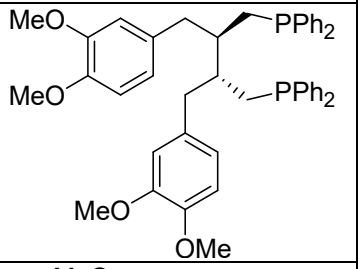
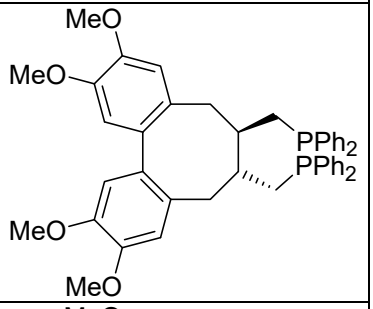
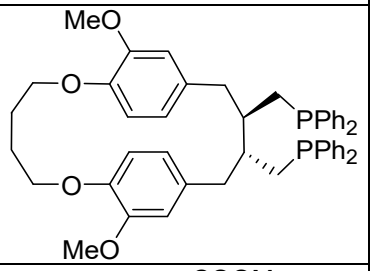
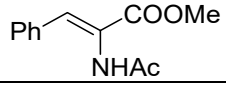
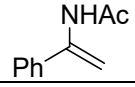
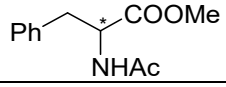
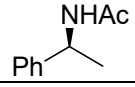
69	
70	
71	
72	
73	
74	
75	

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