Institut für Chemie
Arbeitsgruppe Prof. Peter

NEW SYNTHETIC APPROACHES TO 8,5'-NEOLIGNANS

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Ljubisa Jovanovic

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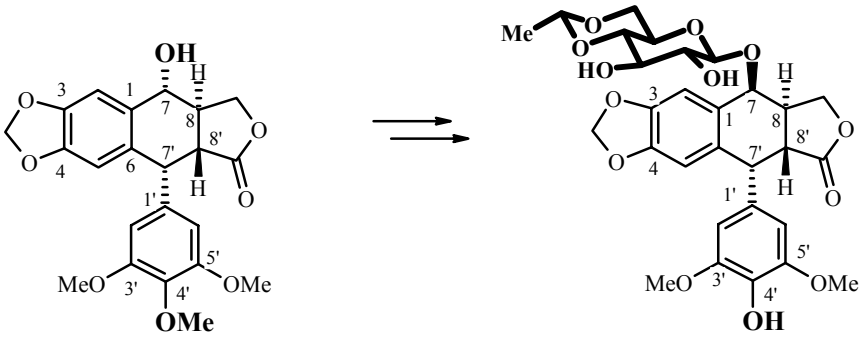
Abbreviations:

9-BBN.....9-Borobicylco[3.3.1]nonane
acac.....acetylacetonate
ATPA……Acids of Trivalent Phosphorus
Bn……...Benzyl
BINAP……...(*R*)-(+)-2,2'-Bis(diphenylphosphino)-1'1'-binaphthyl
bmim..... 1-Butyl-3-methylimidazolium methylsulfate
Bu……...Butyl
COD……..….cyclooctadecane
Cumyl……..…α,α-dimethylbenzyl
dba……..…dibenzylideneacetone
DMA……..*N*,*N*-dimethylacetamide
DMF……..…..Dimethylformamide
DMG……..…Directing Metalation Group
DMSO……..…...Dimethylsulfoxide
DNA……..…..Deoxyribonucleic Acid
D*o*M……..…...Directed *ortho* Metalation Group
dppe……..1,2-Bis(diphenylphosphino)ethane
Et……Ethyl
EtOH……..Ethanol
GC……....Gas Chromatography
HMPT……Hexamethyl Phosphoroustriamine
HPLC.....High Performance Liquid Chromatography
iPr.....2-Propyl
LDA……...Lithiumdiisopropylamide
m-CPBA.....3-chloroperoxybenzoic acid
Me……..Methyl
NMP……..*N*-methylpyrollidone
NMR……..Nuclear Magnetic Resonance
OSEM……....O-trimethylsilylethoxymethyl
PEG…….. Poly(ethylene)glycol
Ph……...phenyl
PTTL……..*N*-phthaloyl–tert-Leucinate
QUINAP……1-(2-Diphenylphosphino-1-naphyl)isoquinoline
*s*BuLi……..…secondary butyllithium
TBAB……tetrabutylammonium bromide
TBS……....*tert*-Butyldimethylsilyl
tert……..…tertiary
TLC……...Thin Layer Chromatography
TMS……..……..trimethylsilyl
TMEDA……..……tetramethyl ethylenediamine
Ts……..……..*para*-toluenesulphonyl
Tf……..……..Triflate
THF……..……..Tetrahydrofuran
RT……..…….Room Temperature

CHAPTER 1 INTRODUCTION

Human health is one of the most important issues that has been addressed in the past and present. Currently, modern medicine, chemistry, biochemistry and pharmacology are trying to prevent, diagnose, treat and understand the reasons, mechanisms and pathways of disorders in the normal function of the human body. Extracts from plants, since they have been available, have been employed for medical treatment with more or less success. In this context, an important field of research is the identification of the active principles from plant extracts, elucidation of their structure and understanding their mode of action.

An example of how natural compounds can become powerful anti-cancer drug is the case of podophyllotoxin (**1**) (Figure 1). This natural compound is a strong but non-selective cytostatic. Transformation of this compound to etoposid[1] (**2**) leads to a new compound with preserved cytostatic properties, but with fewer side effects.



Podophyllotoxin (**1**) Etoposid (**2**)

Figure 1. Structural similarity of podophyllotoxin and etoposid

Chemical substances found in plants are divided into primary and secondary metabolites. Primary metabolites from plants are defined as the necessary substances for the living plant cell (e.g. nucleic acids, proteins and polysaccharides) and they are invariant in the plant kingdom. Secondary metabolites, on the other hand, are compounds such as: lignans, flavonoids, phenols, terpenes, alkaloids, tannins, waxes that plants produce specifically and for other purposes than maintaining the living process (e.g. defence from bacteria or fungi, attraction or repulsion of insects). Due to their role and impact, a more

appropriate name for these substances could be "special metabolites" as suggested by Gottlieb.[2] Wood may contain from 1% to almost 33% of its dry weight as secondary metabolites, and the amount varies with the species. The reasons for the formation of secondary metabolites is still not completely understood, although it is commonly accepted that plants have few mechanisms to excrete undesired by-products of their metabolism (animals have developed efficient excretory systems), so they usually alter these compounds and then store them as „wastes" (secondary metabolites). This hypothesis explains why there are so many different chemical structures within the group of secondary metabolites.[3]

1.1 PHENOLICS

Phenolic compounds are produced via the shikimate, mevalonate and phenylpropanoid pathways (Scheme 1). It is estimated that over 8000 phenolic and polyphenolic compounds are produced by plants. Phenolic compounds are ubiquitous in plant-derived food (e.g. fruits, vegetables, cereals, nuts, wines, whiskies, beer, tea and cocoa). The concentration of these compounds within the plant is dependent on many factors such as species, variety, light intensity, age (degree of ripeness), processing and storage.[4a]

The most important characteristic of the phenolics is their antioxidant activity. Therefore, these compounds (or their metabolites) can directly scavenge reactive oxygen and nitrogen free radical species and chelate metal ions to prevent the generation of oxidizing and cell-damaging species. Potential targets for these species are important biomolecules such as proteins, lipids and DNA. Such effects are implicated in a wide range of diseases including coronary heart disease and certain types of cancers. Other antioxidants present in human metabolic pathways are vitamin E, vitamin C, possibly some carotenoids and a number of enzymes with antioxidant function (e.g. catalase removes H_2O_2 in the cell, glutathion peroxidase metabolises lipid peroxides).

Antioxidant action of these compounds is based on the capacity of the phenolic hydroxyl group to easily form a free radical, loosing one proton and one electron. These free radical species are less reactive than O- or N- derived radicals. However, they react with other reactive free radicals in the surroundings (radical scavenging), thus protecting the cell. Some studies[4b] confirm that many phenolic compounds are capable of scavenging peroxyl radicals, alkyl peroxyl radicals, superoxide, hydroxyl radicals and peroxynitrite in an aqueous and organic environment.[4a]

1.2 LIGNANS AND NEOLIGNANS

Lignin is a polymer that is build of phenylpropanoid units (C_6C_3 structures) and is responsible for thickening and strengthening of the plant cell walls. This highly cross-linked, macromolecular, acid resistant branched polymer, consists of (methoxylated) phenylpropane units linked by other linkages and C–C bonds. The chemical composition of lignin differs according to plant species: lignin from conifers (i.e. soft wood) is derived mainly from coniferyl alcohol with small amounts of sinapyl and *p*-coumaryl alcohol and lignin from dicotyledonous angiosperms (i.e. hard wood) is mainly formed from sinapyl (~ 44%) and coniferyl (~ 48%) alcohol with approximately 8% of *p*-coumaryl alcohol.[5]

Phenylpropanoids are not only precursors of lignin but also of small secondary plant metabolites derived from controlled oxidative dimerisation. This group of secondary metabolites is divided into lignans and neolignans.[6] Lignans are dimers formed from phenylpropanoids linked in a C(8) –C(8′) mode and, depending on their chemical structure, can be classified in four groups (Figure 2):

1) Lignans (e.g. Gualaretic acid (**3**) from *Guaiacum officinale*)
2) Lignanolides (e.g. Matairesinol (**4**) from *Podocarpus spicatus*)
3) Monoepoxilignans (e.g. (–)-Olivil (**5**) from *Olea europea*)
4) Bisepoxylignans (e.g. Pinoresinol (**6**) from *Pinus lavico* and other pines)

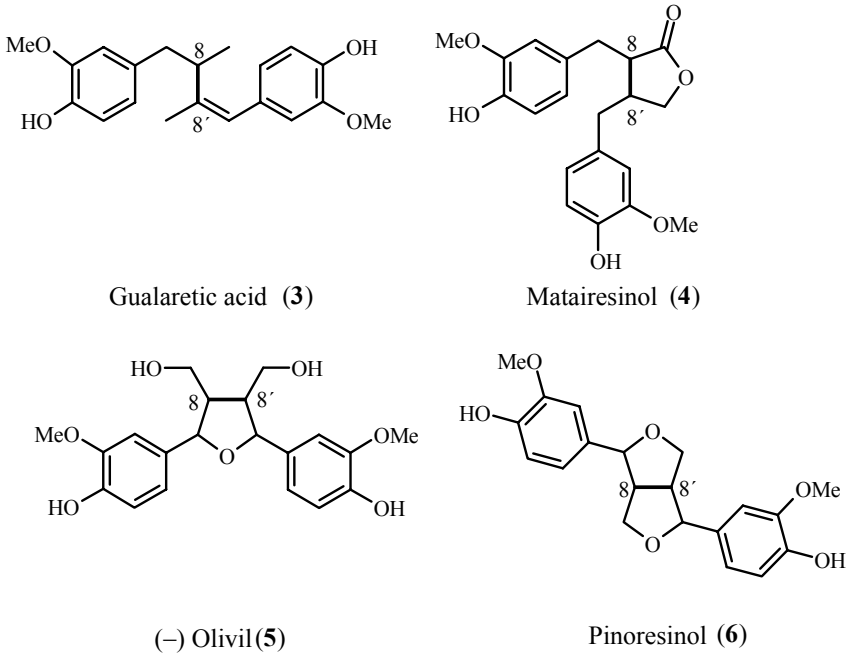
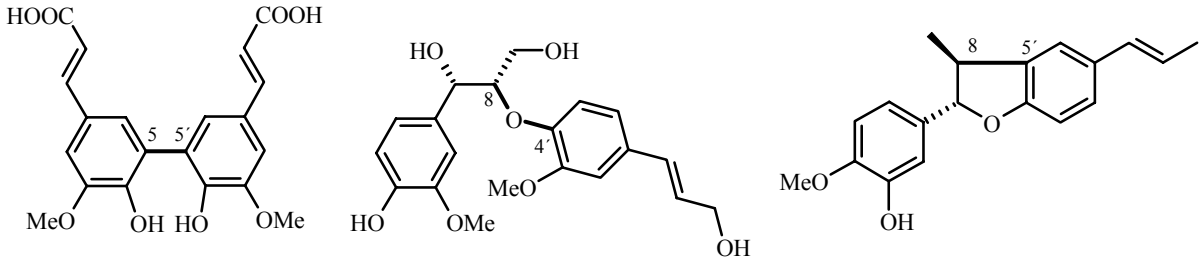


Figure 2. Examples of different lignan groups

Further cyclisation (C(6)–C(7′) bond formation) produces cyclolignans containing tetrahydronaphthalene ring systems (e.g. Podophyllotoxin (**1**)) or naphthalene ring systems (Justicidin B).

Neolignans are connected in a different way than lignans, they have C–C linkages rather than C(8)–C(8′) e.g. C(5)–C(5′) compound (**7**), C(8)–*O*–C(4′) compound (**8**), and C(8)–C(5′) compound (**9**), (Figure 3). They are distributed in the plant families Pineceae and Cupresaceae.



Diferulic acid
5,5′-neolignan
(**7**)

Dilignol
8-O-4′-neolignan
(**8**)

Licarin A
8,5′-neolignan
(**9**)

Figure 3. Examples of neolignans

Dihydrobenzofuran neolignans, 8,5′- neolignans (Figure 4), a large subgroup within neolignans, are found in several families of plants (Myristiceae, Piperaceae, etc.). The interest for these substances has increased in the last few years since it was shown that some dihydrobenzofuran neolignans have cytotoxic,[7] antiviral,[8] antifungal[9] properties, some of them are ACAT inhibitors,[10] or could be used in osteoporosis treatment.[11]

8,5'-Neolignans containing a dihydrobenzofuran skeleton (Figure 4) are the most abundant neolignans in nature. One reason may be the proposed mechanism for the formation of these molecules that includes electrophilic attack of a radical to phenylpropenes (Scheme 3). Initially formed benzyl radical (stabilized) has a phenolic group nearby that takes course in the intramolecular ring closing reaction, yielding neolignans.

Usual substituents:

R^1 = CH_3, CH_2OH, COO-Alkyl, COOH
R^2 = -CHO, -CH=CH-CH_3, -CH=CH-CH_2-OH
R^3 = H, OH,OMe
Ar = 4-HO-Ph-, 4-MeO-Ph-, piperonyl-, 3-MeO-4-HO-Ph-, 3-MeO-4-HO-5-HO-Ph

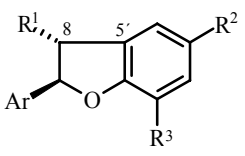
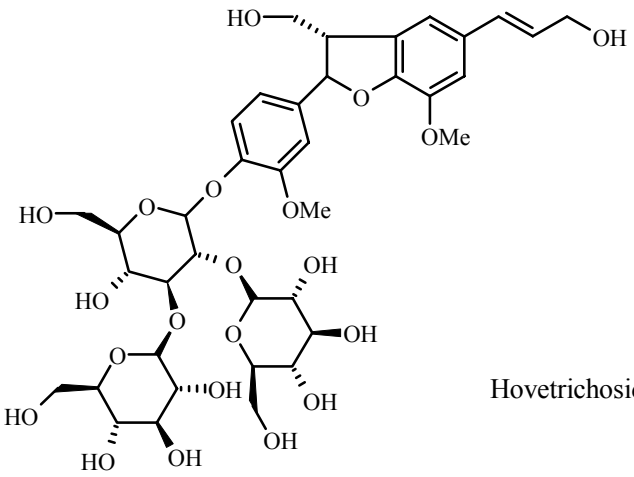


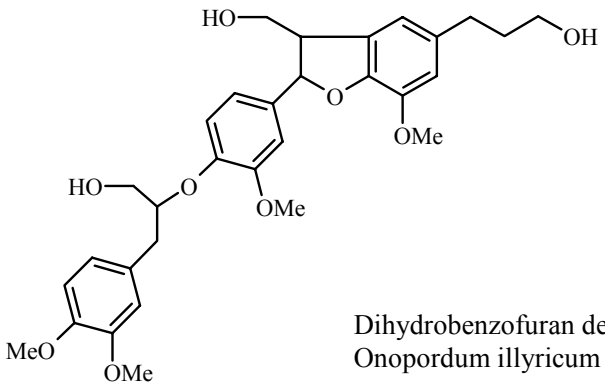
Figure 4. Dihydrobenzofuran skeleton of 8,5′-neolignans

1.3 DIHYDROBENZOFURANS AS A PART OF A COMPLEX MOLECULE

A dihydrobenzofuran moiety is often found as a part of a larger organic molecule in some natural products like hovetrichoside E (**10**) from *Hovenia trichosea* [12] and neolignan derivative (**11**) from *Onopordum illyricum*[13] (Figure 5). The latter plant is widely distributed along the mediterranean coast of Italy where it is called "cardo maggiore". Plants of the genus *Onopordum* have been used in traditional medicine due to their antibacterial, hemostatic and hypotensive properties, presumably derived from compound **11**.



Hovetrichoside E (**10**)

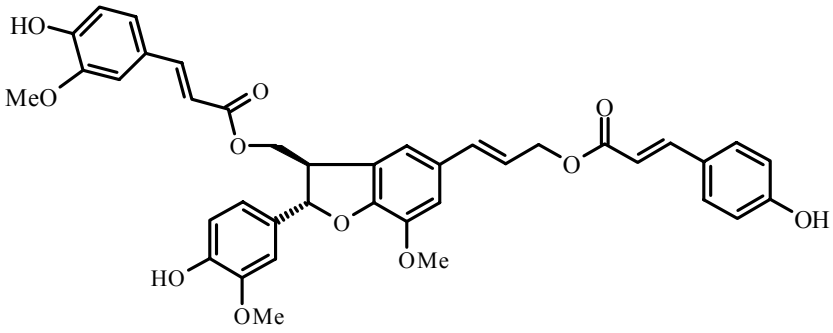


Dihydrobenzofuran derivative from Onopordum illyricum (**11**)

Figure 5. Some natural products containing dihydrobenzofuran moiety

A compound with a dihydrobenzofuran core, consisting of four phenylpropene units

is beohmenan K (**12**)[14] (Figure 6) that is found in kenaf *(Hibiscus cannabinus*). Kenaf is a plant found mainly in Africa, but it is also spread in other geographical areas. This plant has been used as an antidote against chemical poisoning (acids, alkali, pesticides) and venomous mushrooms in traditional medicine.



Boehmenan K (**12**)

Figure 6. Neolignan from *Hibiscus cannabinus*

Compounds **10**-**12** have the dihydrobenzofuran core moiety connected to a phenylpropene subunit. Examples of natural product having the dihydrobenzofuran core moiety connected to a non-phenylpropene subunit are Ephedradine alkaloids, which have a dihydrobenzofuran unit[15] that bridges a seventeen membered lactam (Figure 7) containing a spermine nucleus. Underground parts of *Ephedra* plants are used for preparation of the crude drug „mao-kon“, an antiperspirant drug in oriental medicine.

$R^1 = R^2 = R^3 = H$
$R^1 = R^3 = H$, R^2= OMe
$R^1 = H$, $R^2 = OMe$, $R^3 = Me$
$R^1 = OMe$, $R^2 = R^3 = H$
$R^1 = R^2 = H$, $R^3 = Me$

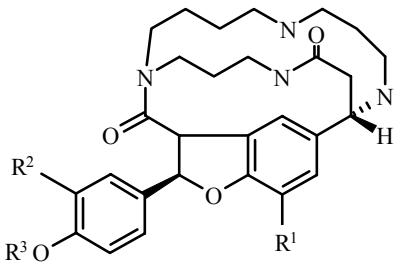
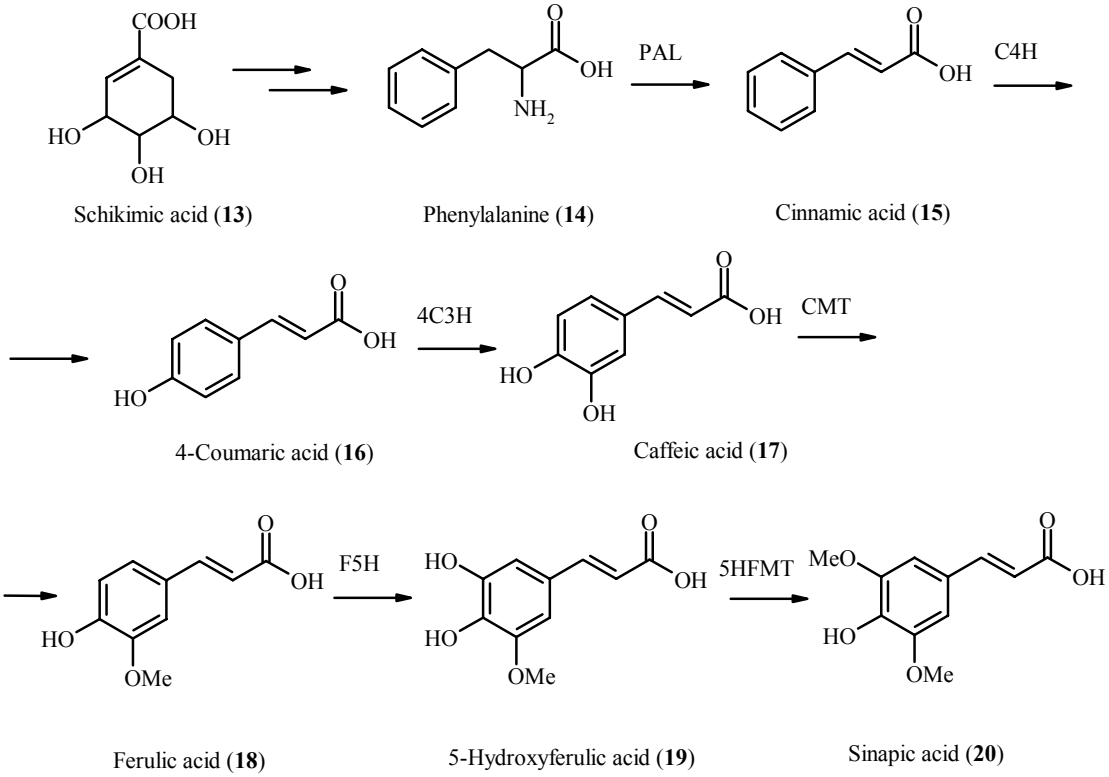


Figure 7. Ephedradine alkaloids having dihydrobenzofuran moiety

1.4 SYNTHESIS OF NEOLIGNANS

1.4.1 BIOSYNTHESIS OF PHENYLPROPANOIDS

Phenylpropanoids are synthesised from shikimic acid by the so-called phenylpropanoid pathway (Scheme 1).



Schikimic acid (**13**) Phenylalanine (**14**) Cinnamic acid (**15**)

4-Coumaric acid (**16**) Caffeic acid (**17**)

Ferulic acid (**18**) 5-Hydroxyferulic acid (**19**) Sinapic acid (**20**)

PAL - phenylalanine ammonia-lyase
C4H - cinnamate 4-hydroxylase
4C3H - 4-coumarate 3-hydroxylase
CMT - caffeate O-methyltransferase
F5H - ferulate 5-hydroxylase
5HFMT - 5-hydroxyferulate O-methyltransferase

Scheme 1. Synthesis of phenylpropanoids from schikimic acid (**13**) in the phenylpropanoid pathway

The first step in the phenylpropanoid metabolic pathway is the stereospecific deamination of phenylalanine (**14**) (formed from shikimic acid (**13**)), which generates the *trans*-double bond of cinnamic acid (**15**). Hydroxylation of the aromatic ring at C(4) generates *p*-coumarate (**16**). Subsequent hydroxylation of the aromatic rings and methylation reactions result in other phenylpropanoic acids (caffeic (**17**), ferulic (**18**), and sinapic acid

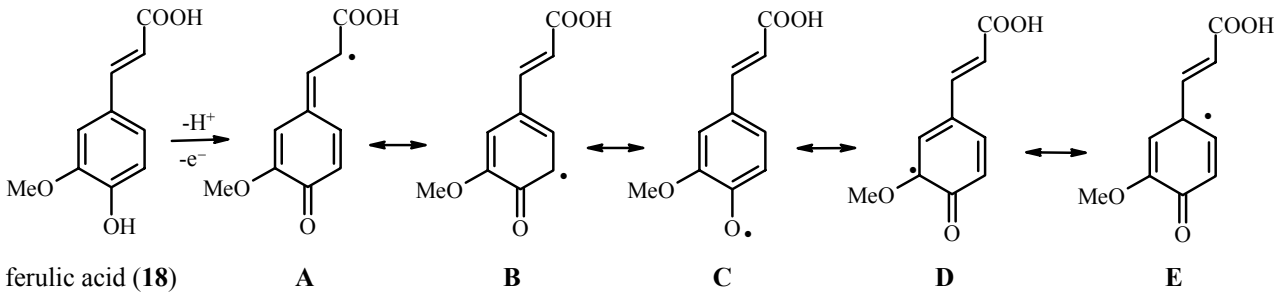
(**20**), respectively).

The phenylpropanoic acids are ubiquitous in plants, for example cinnamic acid exist in almost every plant used for food (fruits, vegetables and grains) and is physically dispersed throughout the plant in seeds, leaves, roots and stems.[16]

1.4.2 BIOSYNTHESIS OF NEOLIGNANS

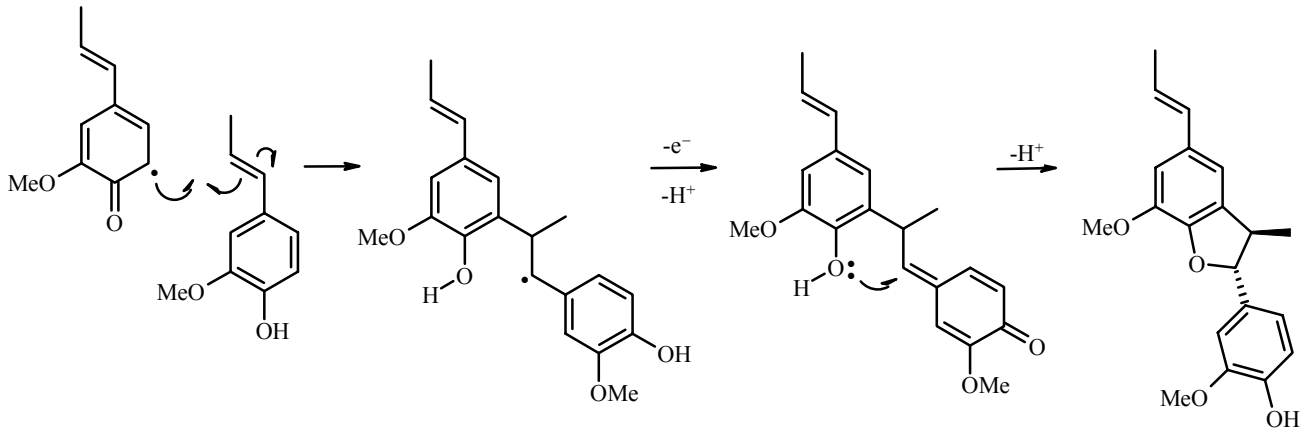
The oxidative dimerisation begins with the formation of a radical species by the abstraction of a proton and an electron from the phenylpropanoid unit. This radical is stabilised by resonance (Scheme 2). There are two different mechanisms that describe formation of C–C bond from the initial radical:

1) Coupling of two radicals leading to dimers (evidence for this mechanism is still lacking[17]). Formation of dimers should be random since mesomeric forms of the radical are equally possible (Scheme 2).[18]



Scheme 2. Stabilized radical derived from ferulic acid (**18**) and resonance structures **A**-**E**

2) An alternative mechanism (Scheme 3) is based on the consideration that highly reactive radicals are generated in low concentrations and on finding that dimers **AB**-**AE** but not **BB** are the most abundant substructures in lignins.[19] Therefore, it is more likely that the dimerisation process involves the electrophilic addition of a radical species to phenylpropenes. The *in vitro* dimerisation of phenylpropenes, either with metal salts, or with enzymes yields dimers such as **AB** or **AC** as major products, and further supports this mechanism. These results can be explained by the formation of a stabilised benzyl radical (**21**) when the double bond is attacked at C(8), forming the compound (**22**) at the end (Scheme 3).

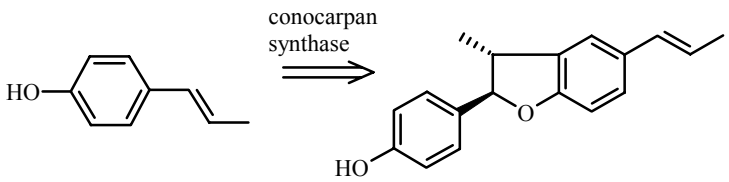


(**21**) (**22**)

Scheme 3. One possible mechanism of the oxidative dimerisation of phenylpropenes

Brunow and Syrjänen have studied the cross coupling of *p*-hydroxycinnamic alcohols with arylglycerol β-arylether lignin model compounds (8–*O*–4' dimers) which represents the phenolic end groups of the growing polymer in the biosynthesis of lignin. They found that cross coupling was surprisingly difficult to achieve, and it can be explained by assuming that this process is governed by a combination of factors such as oxidation potential and radical activity.[20]

In 2001 Kato *et al.* published the first experimental demonstration of the involvement of phenylpropanols in the biosynthesis of neolignans for (+)-conocarpan (**24**) formed in *Piper regnellii.*[21] Labelled L-phenylalanine (U-^{14}C) was used for *in vivo* administration. After its bioconversion to *p*-hydroxypropenylbenzene (**23**), followed by enantioselective coupling of two propenylbenzene units, the (+)-conocarpan (**24**) was formed in 85% ee. The labelled molecules of epiconocarpane were observed in the presence of enzymes obtained from the leaves (Scheme 4).



p- hydroxypropenyl-benzene (**23**)

(+)-conocarpan (**24**)

Scheme 4. Synthesis of (+)-conocarpan (**24**)

It was shown that all the enzymes required for converting L-phenylalanine into phenylpropanoids and eventually to benzofuran neolignans are present in the stems and leaves of *Piper regnellii.* The substrate specificity of this enzyme was evaluated experimentally using *E*-isoeugenol, *p*-coumaric acid (**16**), *p*-coumaric alcohol and *p*-hydroxypropenylbenzene (**23**) as a possible precursor in the coupling reaction. Dimerisation of the product was observed only in the case of *p*-hydroxypropenylbenzene (**23**), suggesting that the enzyme was highly specific for this phenylpropene compound.

1.4.3 CHEMICAL SYNTHESES OF NEOLIGNANS

Lignans represent an abundant group of natural products and many articles and reviews about the their have been published. Neolignans gained more attention when various biological properties were assigned to them, and these ubiquitous substances became very attractive for synthesis. An overview over the strategies for the synthesis of chiral neolignans, in particular 8,5'–, 8,3'–; 8,1'–, 8–*O*–4'–, benzodioxane- and bicyclo [3.2.1]octane neolignans has been published recently.[22]

Some examples of 8,5'-neolignans with a dihydrobenzofuran structure and various side chains are displayed in Figure 8:

R^1	R^2
erythro -CH(OMe)CH(OH)-Me	H
$-CH_2-CH_2-OH$	H
(E)-CH=CH-CH_2-OH	H
(E)-CH=CH-Me	H
-CHO	OMe

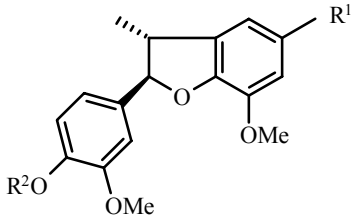


Figure 8. Examples of neolignans with dihydrobenzofuran core structure

Enzymatic reactions that take place in the living organism are very fast, efficient and with defined stereochemical outcome. This is a result of evolution, which, from a chemist's point of view, can be seen as an optimisation process, aiming for maximum precision, straightforward and quick synthesis of defined compound from available starting materials with possibly no side products. Every biosynthetic pathway represents highly optimised chemical process.

For the synthesis of naturally occuring 8,5'-neolignans it could be helpful to use some principles or ideas that nature has chosen to use in the biosynthesis of these compounds. Nature solves this problem in a way that two molecules of phenylpropanoids (two molecules of the same compound or two molecules of phenylpropanoids with very similar characteristics) are coupled in the presence of an enzyme that controls which product is formed (which lignan or neolignan is formed) with high stereospecificity. Both substrate molecules have very similar structure (both are phenylpropanoids, and distinguish themselves only in the substituents in the ring, or, in some rare cases also in the substituent on the double bond). In the synthetic approach without using enzyme in the coupling reaction, it is hard to control which product is formed. The reason for low control is the fact that several reaction pathways are possible, forming several different products. The two oxidants used give rise to different product distribution: hard acid (Fe^{3+}) probably reacts with hard base (phenolate) whereas soft acid (Ag^{+}) does not interact with phenolate and the oxygen may be engaged in a new bond when Ag_2O was used as a base.[23]

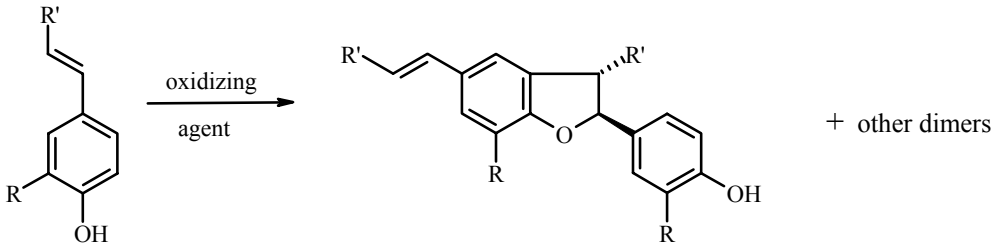
Chemical syntheses of molecules containing the dihydrobenzofuran moiety have been achieved diastereoselectively and enantioselectively.

Following Erdtman's biomimetic oxidation of phenylpropenes,[24] this approach was used in several of diastereoselective neolignan syntheses. Various reagents have been used for the dimerisation of phenylpropenes; most of them can be classified in one of the following groups:

1) Enzymes: (peroxidases,[25] laccases[26]) used in enzymatic oxidations
2) Metal salts (usually Ag_2O[27] and $FeCl_3$[28]) used as oxidants

Other oxidation reagents that were employed in this derivatisation are nitrous acid,[29] oxygen/hν,[30] stable radicals[31] and periodinanes.[32]

The general diastereoselective oxidative coupling reaction is displayed in Scheme 5:



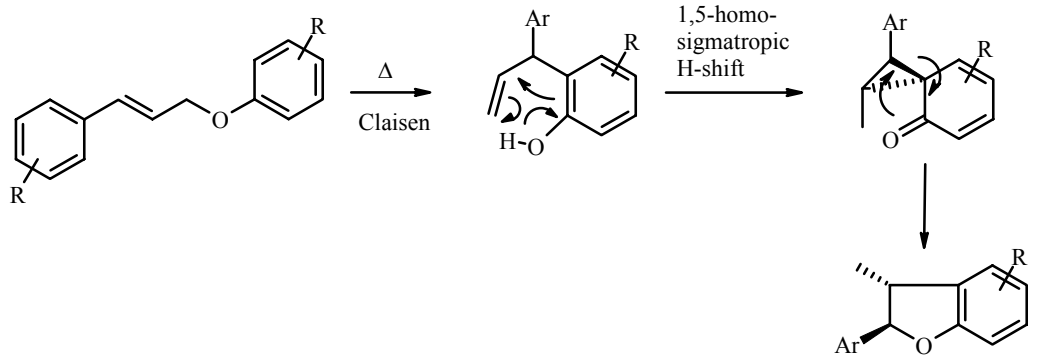
R = H, -OH, -OMe
R' = CH_3, CH_2OH, COOH,
COOMe, COOEt, COOtBu
COOAra, Ara = arabinosyl

Scheme 5. General coupling reaction with phenylpropenes

The major disadvantages of this biomimetic approach are the simultaneous production of a mixture of neolignans (usually 8–*O*–4'-neolignans and 8,5'-neolignans), accompanied by higher oligomers and the requirement that phenolic hydroxy group must be present in the *para* position of the phenylpropene substrate. Due to the latter condition, only few phenylpropenes could be used as substrates. Simultaneous formation of several products brings in focus the problems concerning product purification and decreased yield of the desired product. Furthermore, the ratio of 8–*O*–4'- vs. 8,5'-neolignans in the enzyme catalysed oxidation of phenylpropenes was found to be dependent on the pH value of the solution: the optimal yield and ratio for the synthesis of 8,5'-neolignans was achieved at pH 5.[33] By varying the reaction conditions the 8–*O*–4'-neolignans can become the major product.[34] The combined yield of all dimers was generally found in the range of 10-70%, all isolated dihydrobenzofurans from these reactions had *trans*-configuration. This relative configuration is also dominant among naturally occuring dihydrobenzofurans, although a few neolignans were isolated with *cis*-configuration.[35] After preparation and analysis of the pure *cis*-8,5'-neolignans, most of these structures had to be revised (*cis*-compound can be prepared by hydrogenation of the benzofurane[36]). Comparison of the NMR data of synthesized *cis*- and *trans*-dihydrobenzofurans with those reported for the isolated '*cis*-8,5'-neolignans' showed that previous *cis*-assignments were wrong.

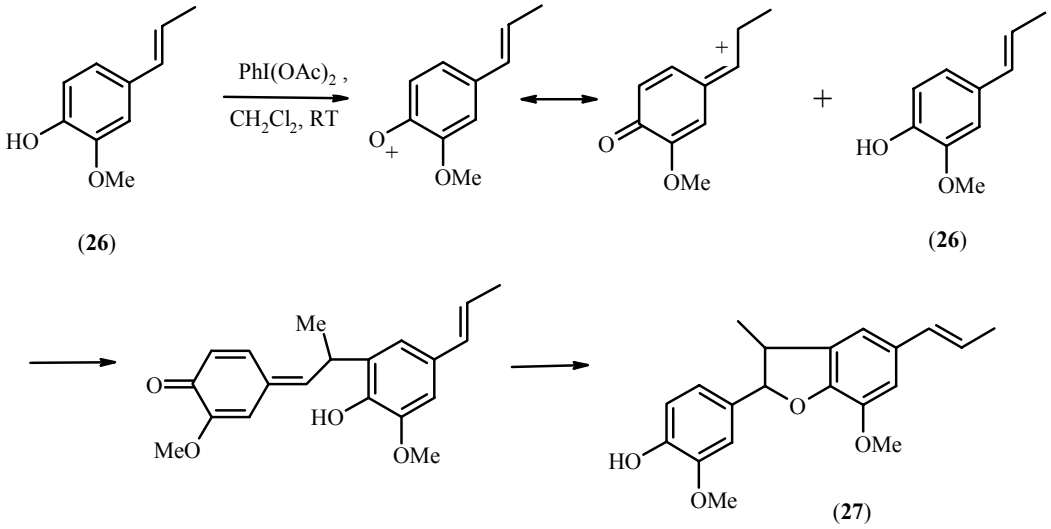
The following reactions have been used in the diastereoselective[22] approaches to the *trans*-dihydrobenzofurans: Schmid rearrangement (abnormal Claisen rearrangement (Scheme 6)), the Lewis acid catalysed rearrangement of chalcone epoxides and the acid catalysed cycloaddition of quinones to phenylpropenes. A radical based cyclisation, directed

metalation at a benzylic methylene group and aromatic Pummerer reaction have also been used for diastereoselective synthesis of the *trans*-dihydrobenzofuran compounds.



Scheme 6. General mechanism of the Schmid rearrangement

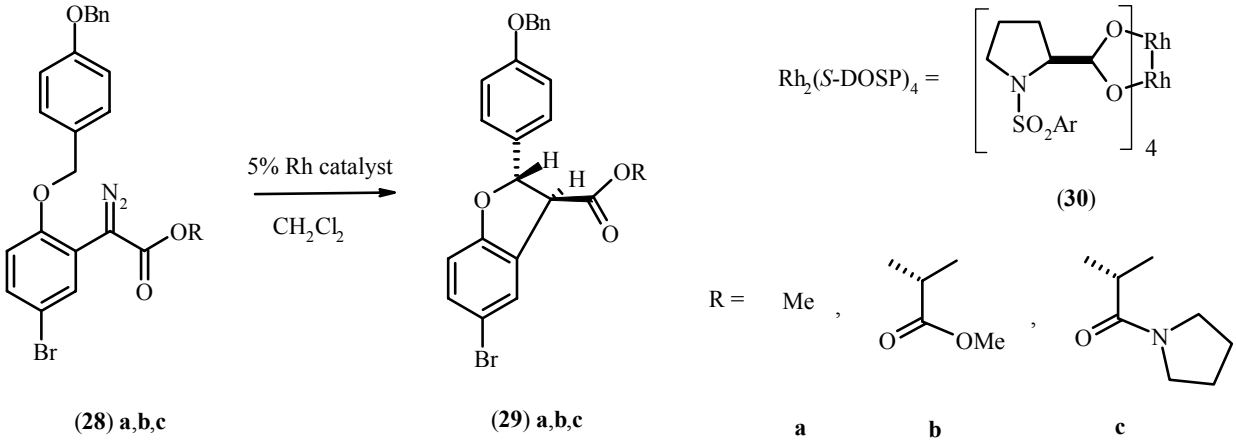
Iodobenzene diacetate was used in a diastereoselective total synthesis of fragnasols A, B and C and dehydrodiisoeugenol starting from isoeugenol[32] **26** (Scheme 7). The key step in this synthesis was the dimerisation of **26** into **27** in dry CH_2Cl_2 at RT in 35% yield.



Scheme 7. Diastereoselective synthesis of **27** using iodobenzene diacetate

Another diastereoselective approach to dihydrobenzofurans using chiral Rhodium-catalyst and chiral auxiliary[37] is shown in Scheme 8 and Table 1. Upon treatment of **28a, b** and **c** (**28b** and **28c** have chiral auxiliaries incorporated in the ester moiety) with Rhodium catalyst (**30**) in CH_2Cl_2 (Table 1), the *trans*-dihydrobenzofuran products (**29a**, **b** and **c**) were formed exclusively (Scheme 8). It was presumed that the increased bulk of the ester moiety

was responsible for the high *trans*-selectivity:



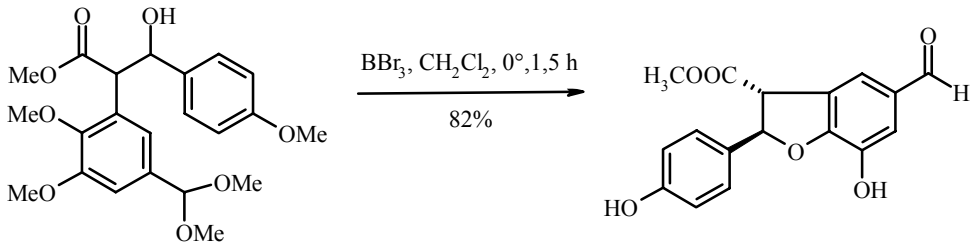
Scheme 8. Synthesis of dihydrobenzofuran derivatives **29a** ,**b**,and **c** with chiral Rhodium catalyst **30**

Table 1. Diastereoselectivity of the Rh-carbenoid mediated intermolecular C–H insertion reaction of **28b** and **28c**

Entry	Rh catalyst [5mol%]	29a	29b	29c
		(trans:cis)	(trans:cis)	(trans:cis)
1	$Rh(OAc)_4$	/	7 : 2	3 : 1
2	Rh(*S*-DOSP)$_4$	3 : 2	5 : 2	8 : 1
3	Rh(*R*-DOSP)$_4$	/	7 : 2	13 : 1

It is interesting to note that both **29b** and **29c** have the same configuration (2*S*, 3*S*) regardless of the chirality of the catalyst (entries 2 and 3, Table 1). Therefore, the asymmetric induction was solely dependent on the chiral auxiliary and not on the catalyst. The highest diastereoselectivity was obtained using a combination of the diazoester **29c** and Rh(*R*-DOSP)$_4$ to afford **29c** in 84% yield and 86% de.

2-Aryldihydrobenzofuran systems have been synthesised using boron tribromide in a key step as simultaneous demethylation and cyclisation reagent (Scheme 9).[38] Cyclisation of **31** under these conditions gave diastereoselectively only the *trans*-dihydrobenzofuran **32**. This one-pot reaction is synthetically very convenient since neither specially dried solvents nor inert atmosphere is necessary.



(**31**) *rac*-(**32**)

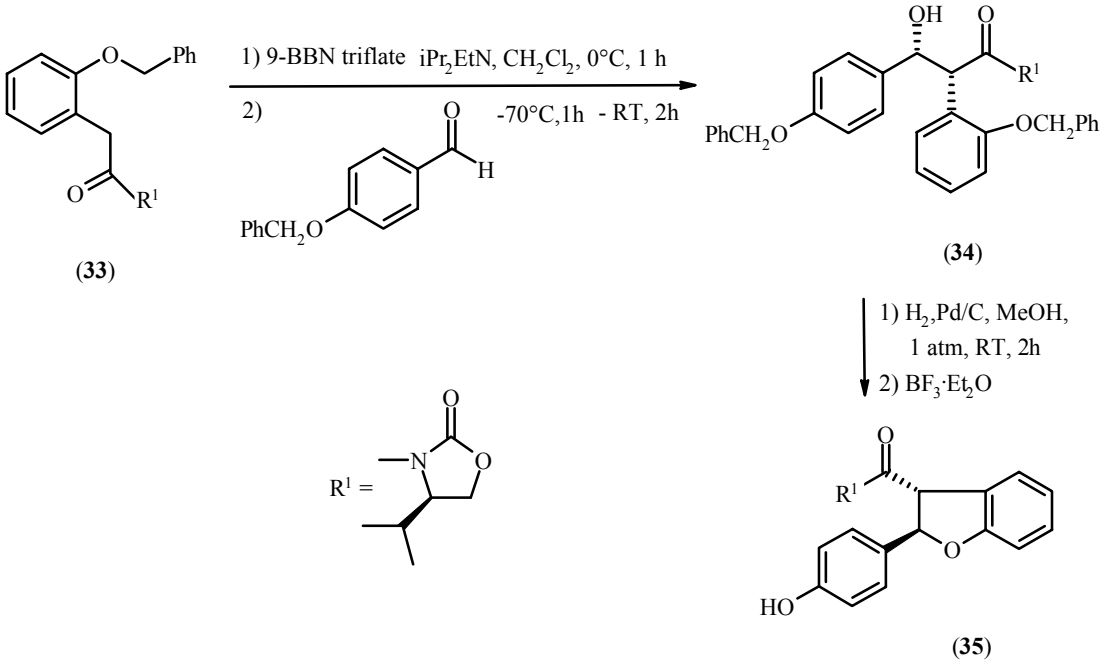
Scheme 9. Demethylation and simultaneous cyclisation with BBr_3

Until now, only a few other studies on the enantioselective synthesis of 8,5'-neolignans are described in the literature. Synthetic approaches were based on asymmetric biomimetic oxidative coupling of achiral phenylpropenes, oxidative coupling of chiral phenylpropenes (chiral auxiliaries were covalently bound to phenylpropenes), a chiral Lewis acid mediated [5+2] cycloaddition, the ring contraction of chiral flavanones and chiral aldol reaction based on Evans's auxiliaries.[22]

Optically active 8,5'-neolignans have also been obtained by resolution of the racemic mixtures by:

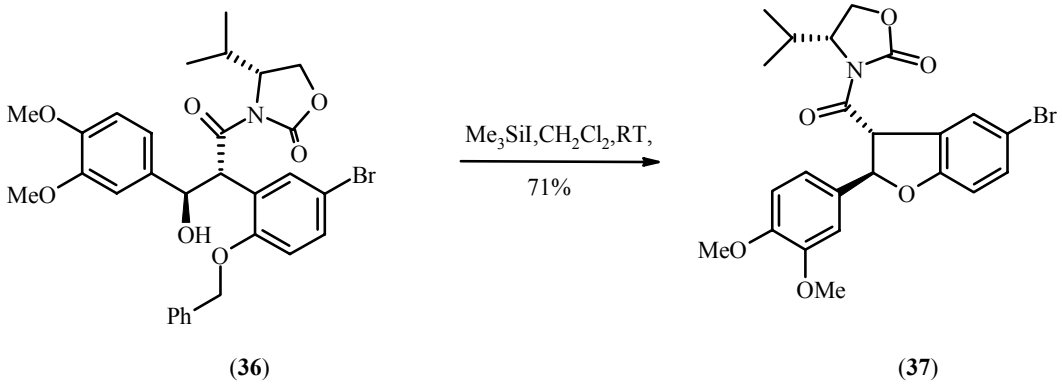
1) HPLC on a chiral stationary phase (Chiracel OD),[21]
2) Derivatisation with chiral auxiliaries followed by chromatographic separation ((–)-camphanic acid, mentoxyacetic acid and Mosher acid were used as auxiliaries)[39]
3) Kinetic resolution of lipase-catalysed monoacetylated dehydroconiferyl alcohol (Scheme 13)[40]

An example of an enantioselective synthesis of the dihydrobenzofuran moiety was published in 1987 first by Hirschfield *et al*.[41] In the key step, enantioselective aldol reaction to **34** was performed using oxazolidinones as chiral auxiliary (in **33**), obtaining **35** with ee > 95% (Scheme 10).



Scheme 10. Enantioselective aldol reaction with oxazolines to **35**

The dihydrobenzofuran segment of ephedradines was also synthesised using iodotrimethylsilane in the key step by Castro *et al.* (Scheme 11). Iodotrimethylsilane was used in excess (2,2 eq) and led not only to debenzylation of **36,** but also to intermolecular cyclisation to form *trans*-dihydrobenzofuran (**37**) as a single diastereomer in good yield.[42]

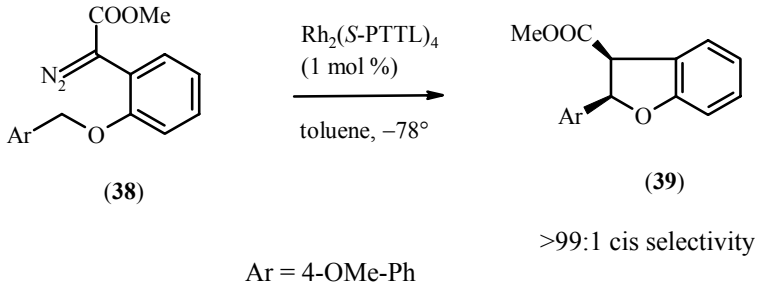


Scheme 11. Debenzylation followed by cyclisation to **37**

The total synthesis of (+)-dehydrodiconiferyl alcohol starting from guaiacol was accomplished within 16 steps in a 16% overall yield by Okazaki and Shuto.[43] The

diastereoselective aldol condensation using Evans´s oxazolidinone was used as a key step. This synthetic method could be suitable for preparing the (−)-isomer of **37** using the other enantiomer of chiral oxazolidinone auxiliary.

The enantioselective synthesis of *cis*-2-aryl-3-methoxycarbonyl-2,3-dihydrobenzo furan (**39**) using Rh(II) catalyst was published recently[44] (Scheme 12). The key was the intramolecular enantioselective C–H insertion reaction of aryldiazoacetate (**38**) with dirhodium tetrakis [N-phtaloyl-(S)-*tert*-leucinate] Rh_2(*S*-PTTL)$_4$, which provided exclusively *cis*-dihydrobenzofuran (**39**) in up to 89% yield and 94% ee.



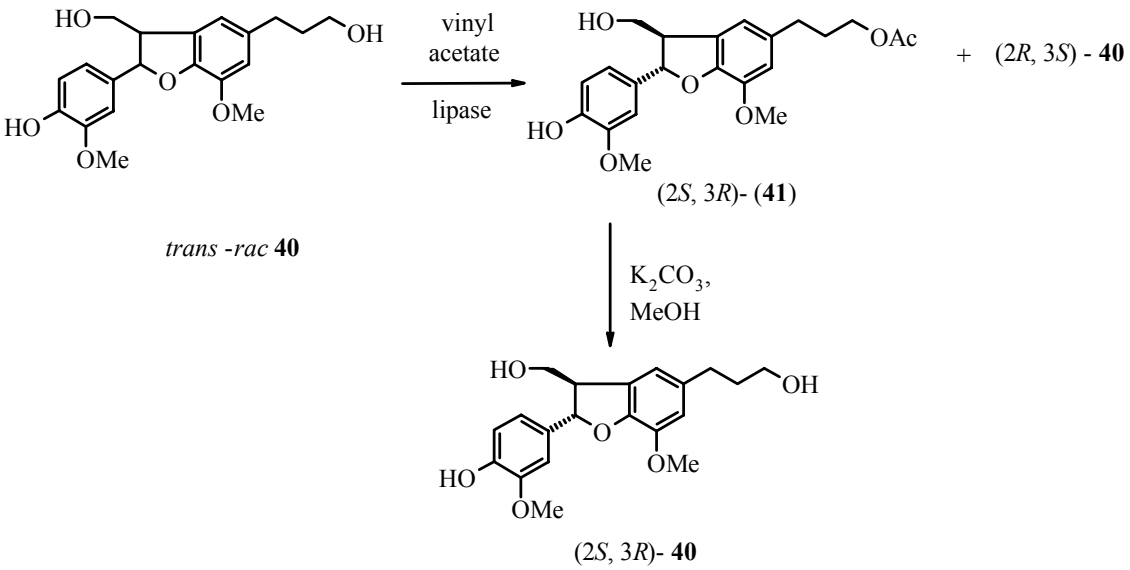
(**38**) (**39**)

>99:1 cis selectivity

Ar = 4-OMe-Ph

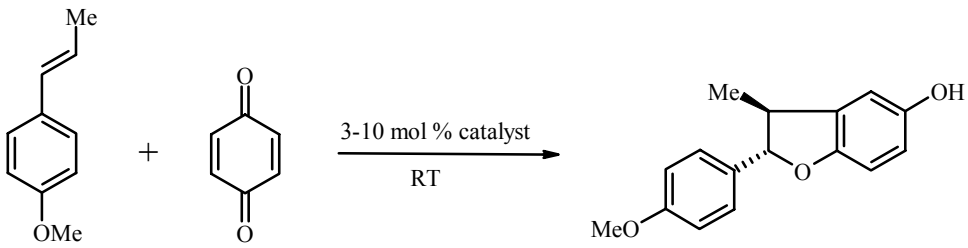
Scheme 12. Rhodium catalysed synthesis of *cis*-dihydrobenzofuran (**39**)

The first report of an enzymatic reaction used to obtain optically pure dihydrobenzofuran neolignans was published by Lemiere *et al.* in 2001.[40] The product was racemic mixture and the chiral resolution was performed with lipase. Ten different lipases were screened for enantioselectivity in the acetylation reaction in organic solvent. The best results were obtained with porcine pancreas lipase and *Candida cylindricea* lipase. *Pseudomonas cepacia* and *pseudomonas fluorescens* lipases gave enantiomerically pure starting materials, albeit in low yield (26-30%). *Candida cylindricea* lipase (immobilised) provided, after optimisation of the conditions, *trans* alcohol (**40**) in good yield and reasonable ee (75% yield with 77% ee) (Scheme 13):



Scheme 13. Kinetic resolution of **40** with *Candida cylindricea* lipase

Optically active 2,3-dihydrobenzofuran **44** was synthesised[45] in the iron (III)-catalysed cycloaddition reaction of alkenes and quinone **43** (Scheme 14). Ionic liquids have also been employed as the solvent in the reaction of quinone **43** and anethole **42** (Table 2, entries 1 and 2) and it resulted in improved selectivity and yielded **44**.[62] The [3+2] cycloaddition reaction between **42** and **43** can also be catalysed with $InCl_3$ or I_2[46] (Table 2, entries 3 and 4):



42 **43** **44**

Scheme 14. [3+2] cycloaddition reaction with quinone

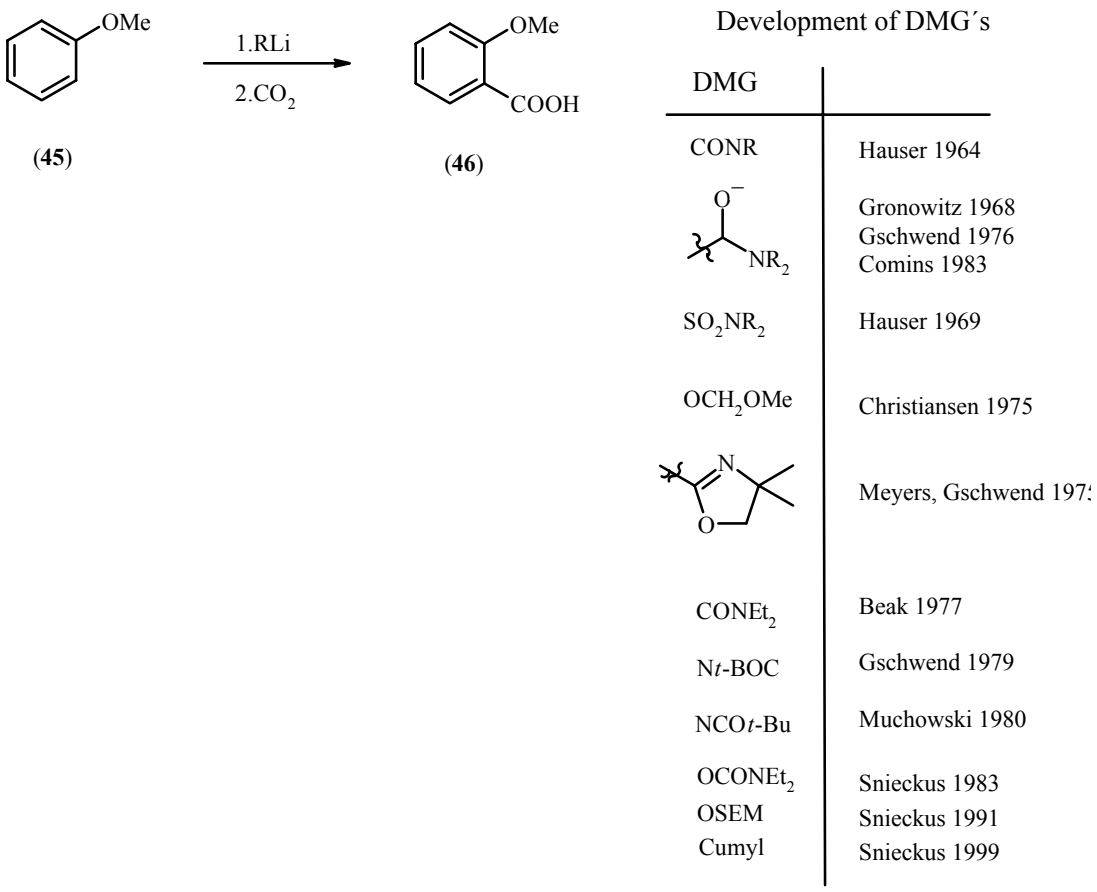
Table 2. Yield and *trans* : *cis* ratio of **44** formed in the reaction displayed in Scheme 14

Entry	Catalyst [mol %]	Solvent	Yield 44 [%], *trans*:*cis*
1	$Fe(BF_4)\cdot 6H_2O$	$[bmim]BF_4$	68 %; 43 : 1
2	$Fe(BF_4)\cdot 6H_2O$	$[bmim]PF_4$	98 %; 11 : 1
3	10 mol % $InCl_3$	CH_2Cl_2	89 %
4	5 mol % I_2	CH_2Cl_2	85 %

The reactions between alkene and quinone were performed at room temperature, they enable construction of the dihydrobenzofuran ring in one step with high yield, but there are also some drawbacks: one of the substrates must be quinone, meaning that the substitution pattern in the formed product cannot be altered and this limits the scope of the reaction.

1.4.3.1 The synthesis of dihydrobenzofuran compounds *via* directed α metalation

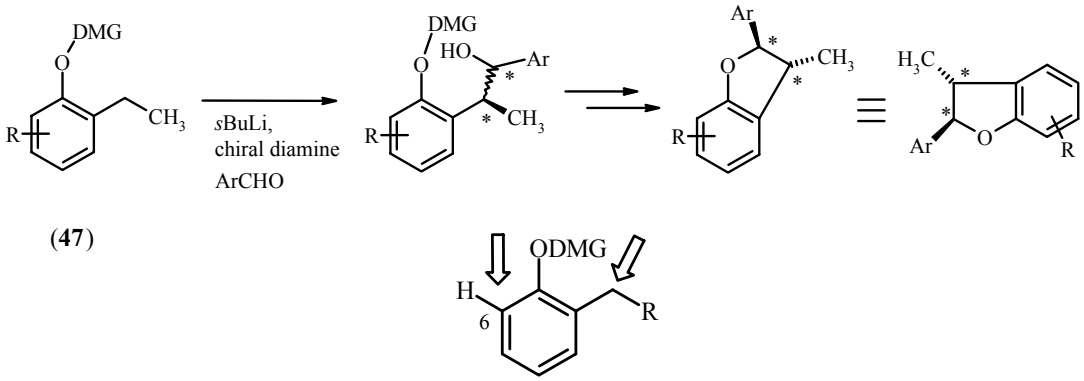
The ability of some groups on an aromatic ring to selectively direct metalation into the *ortho*-position of the aromatic ring was discovered by Gilman and Wittig (Scheme 15) around the 1940´s.[47] These groups are called directed metalation groups (DMG) or directed *ortho*-metalation groups (D*o*M-groups). A short chronological overview in the development of DMG´s is presented in Scheme 15: [48]



Scheme 15. Directed *ortho*-metalation: discovery and development

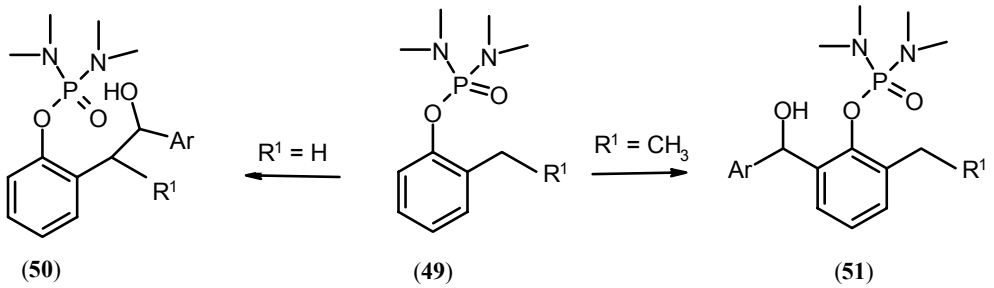
There are two possible deprotonation sites in the metalation reaction of *o*-alkylphenol derivatives bearing a DMG (**48**): *ortho*-deprotonation (ring) and α-deprotonation (side chain). The regioselectivity in this reaction has not been fully investigated up to now.

This general approach to dihydrobenzofurans was published using the bis-N,N-(dimethylamino)phosphoryl group[49] as a directing group (**47,** Scheme 16), but the problem of finding a DMG that would regioselectively give benzylic anions in the alkyl side chain of compounds such as (**48**) (R≠H, Scheme 16) after deprotonation was only very recently resolved.[50]



Scheme 16. Proposed synthetic approach to optically active dihydrobenzofurans via *o*-alkylphenol derivatives

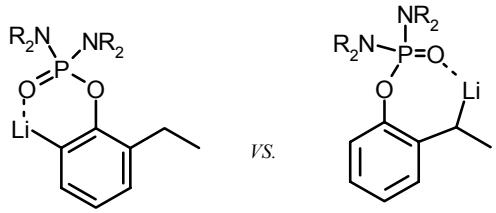
It has been shown that the length of the alkyl side chain connected to an aromatic moiety of **49** has a strong influence on the regioselectivity: [49] when the *ortho* position in the aromatic ring was substitutied with a methyl group (R^1=H), the benzylic anion was generated (α-deprotonation) leading to **50** whereas when the *ortho* position was substituited with ethyl group (R^1=CH_3) the ring deprotonation was observed giving **51** after work-up (Scheme 17).



Conditions: THF, –105°C, ArCHO

Scheme 17. Influence of the length of alkyl side chain on regioselectivity of deprotonation

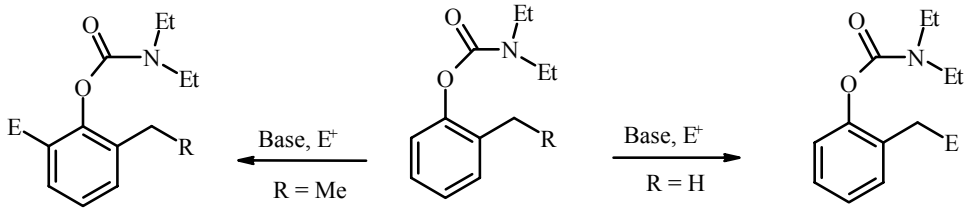
The regioselectivity is determined by the ability of the DMG to stabilise anions generated under the reaction conditions. For R = R^1 = H, discrimination between ring- and benzylic- anion positions is reflected through stabilities of the 6-membered transition state (**51**) formed in the case of ring deprotonation and the 7-membered transition state (**53**) formed in the case of benzylic deprotonation (Figure 9). 6-membered rings are generally more stable and have less strain than 7-membered rings.



(**52**) (**53**)

Figure 9. Lithiumorganyl intermediates formed after ring- and benzylic- deprotonation

The same regioselectivity that was dependent on the alkyl side chain was also observed with carbamates (**51**) as DMG [51]:



(**55**) (**54**) (**56**)

60 % (Base = sBuLi)
33 % (Base = LDA)

30 % (Base = *s*BuLi
66 % (Base = LDA)

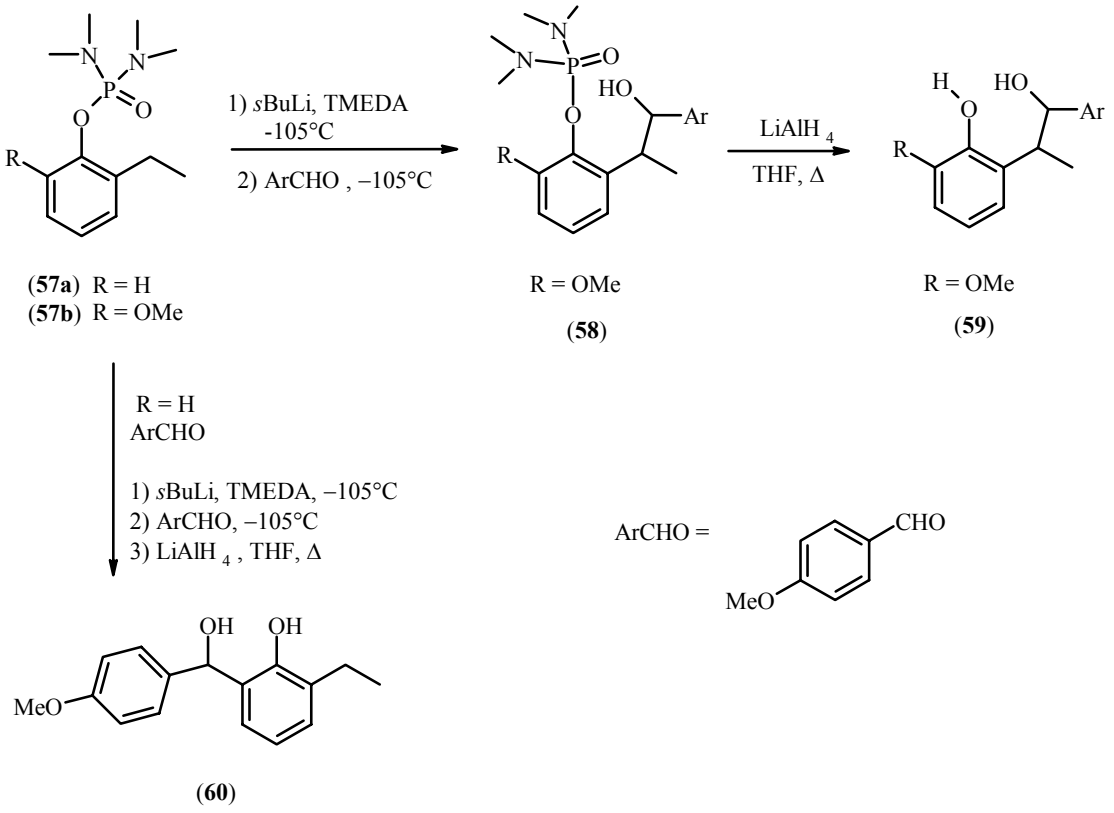
Scheme 18. Regioselectivity of deprotonation with carbamates as DMG

As has been displayed in Scheme 18, the yield of α-alkylated product was significantly dependent on the base employed (for *s*BuLi: 30% α-alkylation (**56**), 60% *ortho*-alkylation (**55** - ring alkylation), for LDA: 66 % α-alkylation (**56**), 33 % *ortho*-alkylation (**55**). LDA, a sterically more hindered base, was more regioselective and gave more α-alkylated product (**56**).

Increased sterical bulk in the case of the ethyl side chain ($R^1 = CH_3$) could be the reason for the preferred ring lithiation. The lone pair from the DMG can stabilise anions formed from ring deprotonation with Li-amine species better than anions formed from deprotonation in the benzylic position (**48**, Scheme 16).

A general synthetic approach to 2-aryl-2,3-dihydrobenzofurans *via* a regioselective lithiation of *ortho*-tolyltetramethyl phosphorodiamidates was developed by Watanabe *et*

al.[49] (Scheme 19). *Ortho*-tolyltetramethyl phosphorodiamidate (**57 a**) was regioselectively lithiated with *s*BuLi in THF at −105°C to form benzylic lithioorganyl, which upon addition of aromatic aldehyde reacted to provide 1,2-diarylpropanol derivative **59**. Addition of 1,2 eq TMEDA as a lithium coordinating reagent to the reaction mixture led to improved yield: 69% compared with 43% yield when TMEDA was omitted.

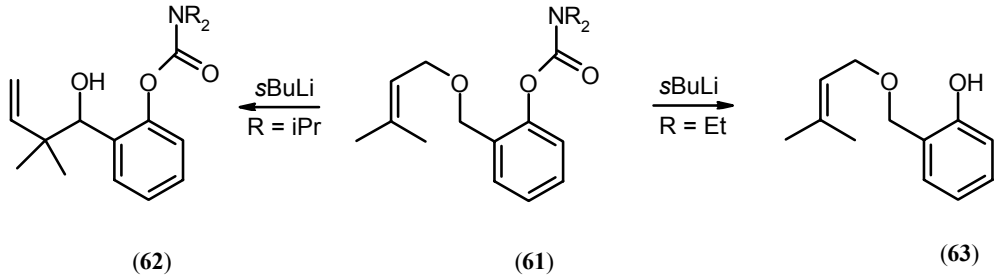


Scheme 19. Regioselective lithiation of *ortho*-tolyltetramethyl phosphorodiamidates **57a** and **57b**

Reductive removal of the phosphoryl group with $LiAlH_4$, followed by acidic treatment afforded 2-aryl-2,3-dihydrobenzofurans. Using this approach, natural neolignans *rac*-licarin B and *rac*-carinatol were synthesised. [49]

In the reaction of **57a** and *p*-anisaldehyde as electrophile under standard conditions (*s*BuLi, TMEDA, THF, −105°C, 1h), the obtained product was dephosphorylated ($LiAlH_4$, THF) and formed **60**. The compound **60** was formed from the ring deprotonated species in 25% overall yield. With compound **57b**, having a methoxy group in the *ortho* position of the aromatic ring, side chain deprotonation (α-deprotonation) was observed giving **58**. This compound gave **59** after dephosphorylation (Scheme 19).

The carbamoyl group has also successfully been used as DMG. Kawasaki and Kimachi[52] have shown that the α-directing ability of the N-substituted carbamoyl-alkyls (**61**) is strongly dependent on the alkyl-residue in the DMG (Scheme 20): Diisopropylcarbamat derivative formed allylalcohol **62** after Wittig rearrangement, and diethylcarbamat derivative formed deprotected phenol **63** under the same conditions.



(**62**) (**61**) (**63**)

Scheme 20. Influence of the alkyl-chain on the outcome in the reaction of N-substituted carbamoyl-alkyls with *s*BuLi

While the present project was carried out, it was published that compounds of similar structures (**64-68**, Figure 10) are very sensitive towards oxidation and hydrolysis, and that chromatographic purification was possible only in some cases.[53] These compounds have either a heteroatom (**64-66**) or aromatic carbon (**67-68**) in the *ortho* position. The latter two compounds were found to be stable only as the corresponding palladium complex.

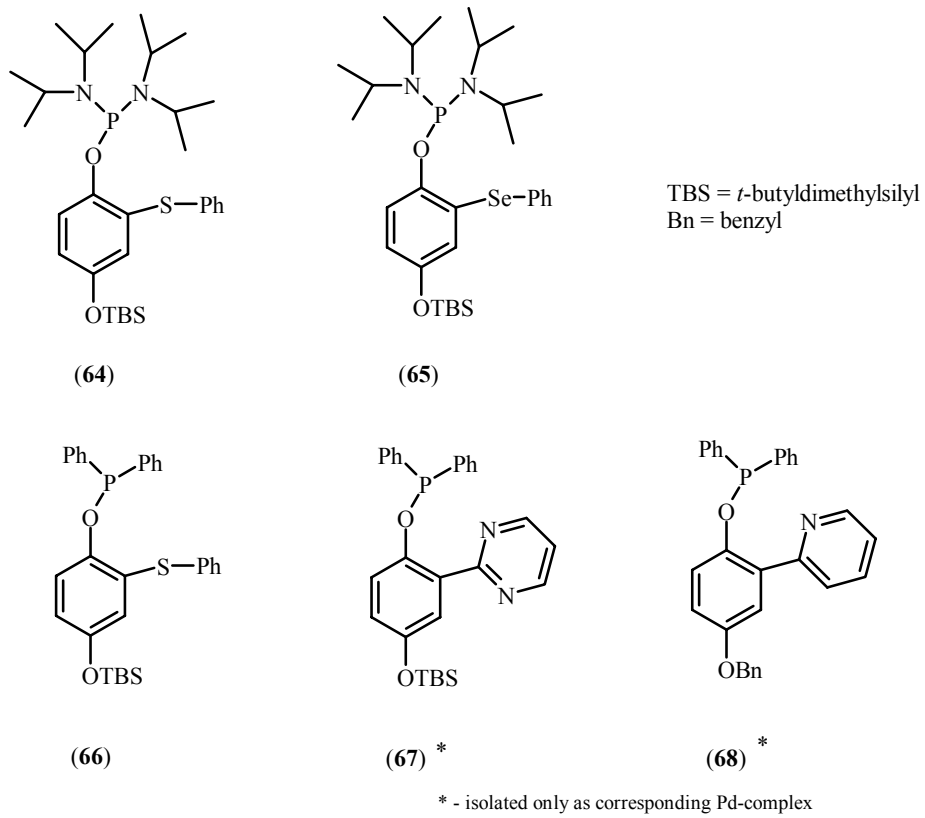
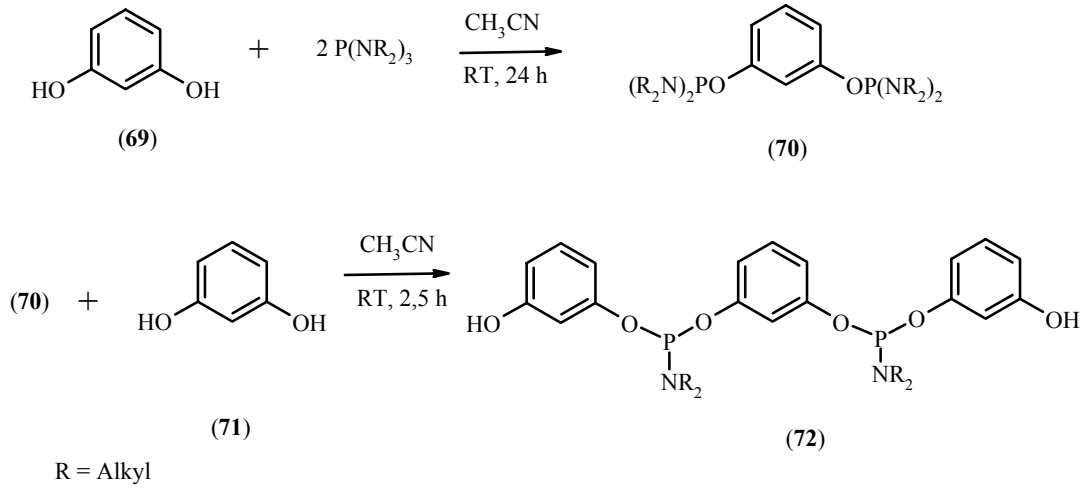


Figure 10. Some isolated phenol derivates with phosphorous DMG-s

1.4.3.1.1 Some possible side reactions in the preparation of phosphamidates

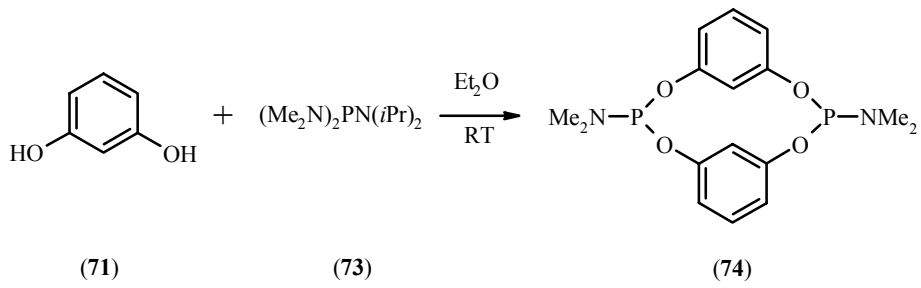
The ability of the dialkylamino group to act as a leaving group when attached to phosphorous atom was described in several studies. For example, reactions in which dialkylamino group shows this leaving-group behaviour in the presence of resorcinol (**69**) have been published by Nifantyev *et al.* in 1998 (Scheme 21).[54] This reaction was performed in CH_3CN at room temperature within 24 h. After the formation of compound **70**, reaction with another equivalent of resorcinol (**69**) in CH_3CN (at room temperature) for 2,5 h gave compound **72**. This compound was formed after the nucleophilic attack of resorcinol on phosphorous atom of **70** and the leaving of the dialkylamino group.



Scheme 21. Reaction between resorcinol (**69**) and symmetrical phosphorous triamide

Compound **72** has phenoxy groups and phosphamide functions, two functional groups that can generally interact. The authors claim that they have found conditions wherein these groups do not interact, but these conditions have not been published.[54]

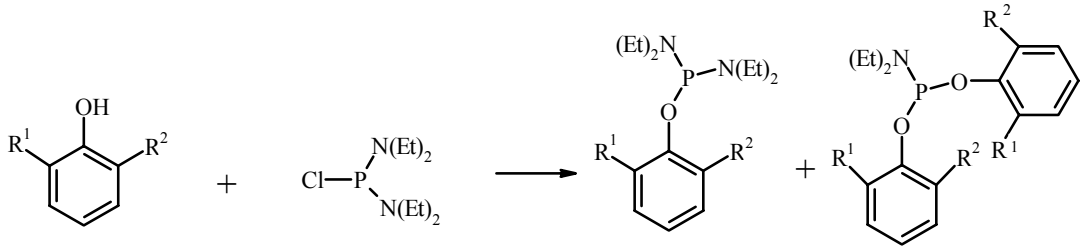
The effect of the isopropyl group on phosphorylation of phenols with phosphorous triamides was also studied by Nifantyev *et al*.[55] The reaction between resorcinol (**69**) and the unsymmetrical triamide bis(dimethylamino)isopropylamino phosphorous triamide (**73**) was studied. The authors suggested that although it is heavier and less reactive, the diisopropylamino group in **73** is substituted prior to a dimethylamino group[56] forming exclusively **74** (Scheme 22).



Scheme 22. Reaction of resorcinol (**71**) with unsymmetrical phosphorous triamide (**73**)

Eritja *et al.* have found[57] that bulky substituents in the *ortho* position of the phenol can have a strong influence on the yield of the reaction shown in Scheme 23. Using tertiary amines as a base (Et_3N, $(iPr)_2EtN$), the alkylammonium halide was formed in the course of

the reaction. This alkylammonium halide was difficult to remove completely and, as a consequence, these salts further activated the phosphoramidite to yield side products, namely bis(*O*-aryl)-N,N-diethylphosphoramidite (compounds **82**, **83**, **84**). In order to avoid these problems caused by alkylammonium halide, EtONa was used as a base to generate sodium phenolate, but even this approach failed to yield exclusively **79**, **80** or **81** with phenols **75**, **76** and **77** having bulky substituents in the *ortho* positions (Scheme 23).



(**75**) R^1=H, R^2=Br
(**76**) R^1=H, R^2=Me
(**77**) R^1=R^2=Me

(**78**)

(**79**) R^1=H, R^2=Br
(**80**) R^1=H, R^2=Me
(**81**) R^1=R^2=Me

(**82**) R^1=H, R^2=Br
(**83**) R^1=H, R^2=Me
(**84**) R^1=R^2=Me

Scheme 23. Formation of the side products **82**, **83**, and **84** in the reaction with phenols **75**, **76** and **77**

This is an unexpected result since *O*-arylphosphordiamidites have been synthesised[57] in a good yield (40-95%) from sodium phenolates and bis(N,N-diethylamino)chlorophosphine (**78**).

With the sodium phenolates derived from compounds having at least one unsubstituted *ortho* position (2,4-dinitrophenol, 2,4,5-trichlorophenol, 4-nitrophenol, 4-bromophenol and phenol) or sterically small substituents in *ortho* positions (pentafluorophenol, pentachlorophenol), the corresponding *O*-arylphosphordiamidites were synthesised in 75-90% yield. *O*-arylphosphordiamidite derived from pentachlorophenol was accompanied with bis(*O*-aryl)phosphoroamidite.

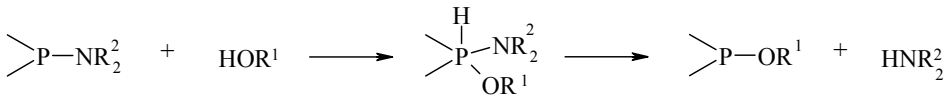
When the phenolates were prepared from derivatives having one sterically large substituent or with both *ortho* positions substituted (2-bromophenol, 2-methylphenol and 2,6,dimethylphenol), significantly lower yields of corresponding *O*-arylphosphordiamidites were obtained (40-74%) in each case accompanied with corresponding bis(*O*-aryl)phosphoroamidites.

This example illustrates that there is an influence of the substitution pattern in the *ortho* position (more accurately the size of the substituent in the *ortho* position) on the

formation of the side product bis(*O*-aryl)phosphoroamidite. A large substituent in the *ortho* position of the phenolate favours the formation of the bis(*O*-aryl)phosphoroamidite.

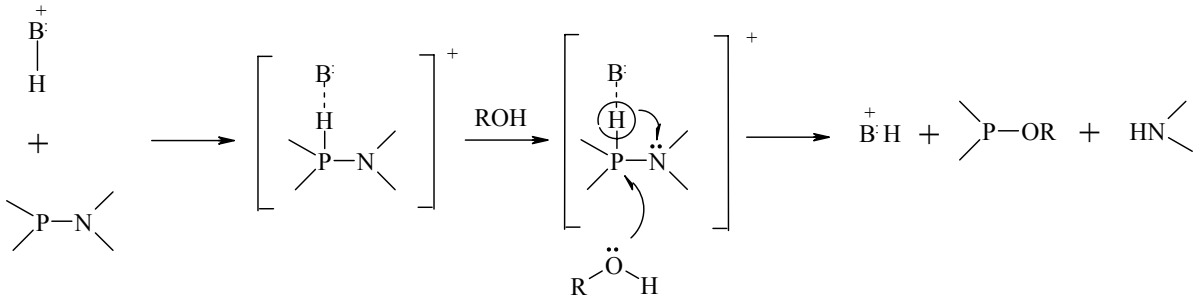
The phosphorylation reaction of alcohols and phenols with amides of acids of trivalent phosphorous (ATPA) was discovered in the late 1950's[58] and it represents an unusual phosphorylation method. The importance and scope of this method were not realised right away. Nowadays, ATPA has aplications in the chemistry of nucleic acids or phospholipids.

The compounds **82**, **83** and **84** can be seen as products of the phosphorylation of compounds **75**, **76** and **77** with an initially formed product. A proposed mechanism for this reaction is the "addition-elimination" mechanism (Scheme 24):[59]



Scheme 24. Proposed mechanism for the phosphorylation reaction of alcohols and phenols

Phenolysis of ATPA is catalysed by alkylammonium halides,[60] formed as the side product in the reaction with amine bases. The proposed mechanism is shown in Scheme 25:



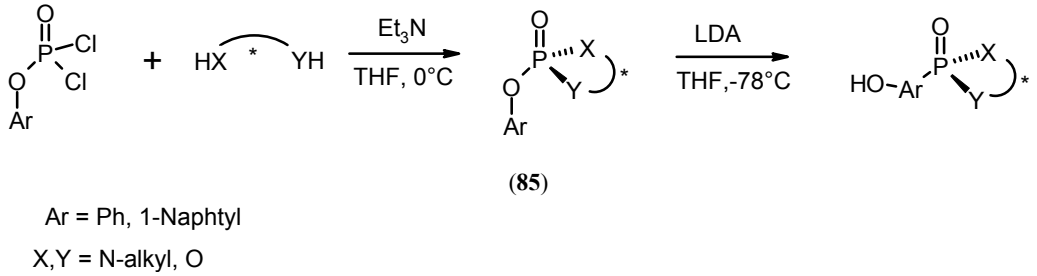
Scheme 25. Proposed mechanism for amine hydrochoride catalysed phosphorylation of alcohols and phenols

Nevertheless, this is not a general reaction since the cleavage of the phosphamide bond in ATPA by ammonium halides is very dependent on the alkyl rest. Phosphoric hexaethyltriamide cleaves much less efficiently than hexamethyltriamide and higher amides do not react with ammonium halides on the preparative scale.[59]

It has been found in numerous cases that the amido groups in phosphorous triamides can be replaced stepwise by alkoxy[61] or aryloxy groups.[62] Triamides prove to be more reactive than diamides, while diamides are more reactive than monoamides.

Bis(N,N-diisopropylamino)chlorophosphine was used for the synthesis of phosphoramidites and H-phosphonates of d-nucleosides, and for the formation of 3′-5′-internucleotidic phosphonate bonds.[63] The 3′-phosphoramidites are suitable building blocks for solid-phase DNA synthesis.

It has already been described that P–O to P–C rearrangement[64] with complete retention of configuration on phosphorous atom occurs upon treatment of compounds **85** with LDA at −78°C (Scheme 26):



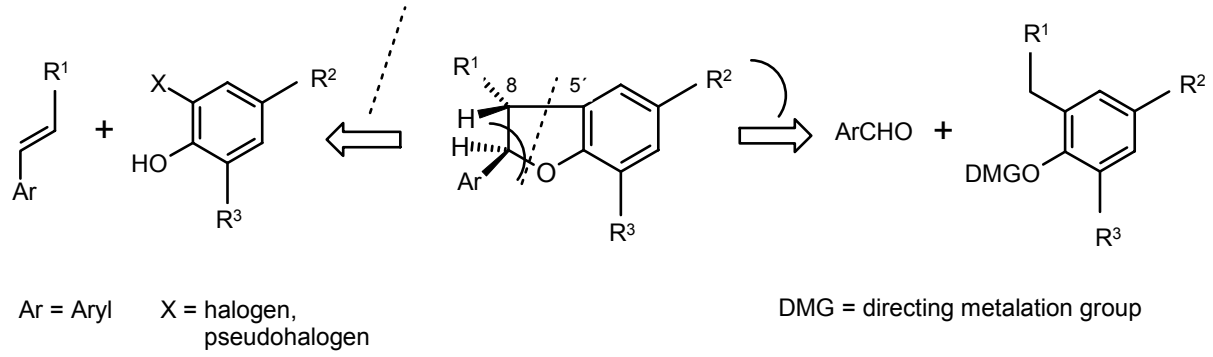
Scheme 26. Proposed mechanism of P–O to P–C rearrangement in the presence of LDA

O-hydroxyarylphosphine oxides, formed after P–O to P–C rearrangement (**85)**, have a basic (P=O) and an acidic (OH) site close to each other. They have found application as catalysts in the asymmetric addition of diethylzinc to aromatic aldehydes[65] and are efficient ligands for the titanium enantioselective trimethylsilylcyanation of aromatic aldehydes.[64]
The synthesis of Bis(dialkylamino)phosphamidates represents a real challenge, since these compounds are very sensitive towards hydrolysis (bis-amidite group is instable and shows extreme acid lability[63]) and some side products are formed in the course of the reaction.

CHAPTER 2 AIM OF THE WORK

Currently published syntheses of *trans*-dihydrobenzofurans are multistep procedures that are time consuming and provide the product in low yield. Furthermore, all dimerisation reactions, either in the presence of enzymes or mediated by metal salts, yield dimers consisting of two units of the same phenylpropene compound, narrowing substantially the substitution pattern.

The aim of this work is to design a general synthetic strategy for *trans*-dihydrobenzofurans (8,5´-neolignans). The synthesis should give the target molecules diastereo- and enantioselectively. Two principle routes were followed (Scheme 27): the first strategy was the enantioselective deprotonation at the α-carbon of the *o*-alkyl phenols in the presence of a (chiral) diamine and *s*BuLi, the second strategy was the [3+2] cycloaddition reaction.



Scheme 27. Retrosynthetic analysis of the compounds having dehydrobenzofuran moiety

Since the fundamental work of Hoppe and Beak, it is known that diamines coordinate to Li^+ species and are stabilising Li-organyls. When chiral diamines are employed, they transfer the chiral information to the carbanion. The addition of such anions to the carbonyl group of aromatic aldehydes, followed by cyclisation, should result in the generation of chiral neolignans.

A one-step 3+2 type cycloaddition should be possible by a transition metal catalyzed ring closure reaction of appropriate substrates. Thus, the second approach using transition metals and chiral ligands should yield chiral dihydrobenzofurans in one step. Starting materials for this approach were chosen so that R^2 allows transformations in the side chain (R^2 = CHO, Cl), enabling access to a variety of neolignan derivatives.

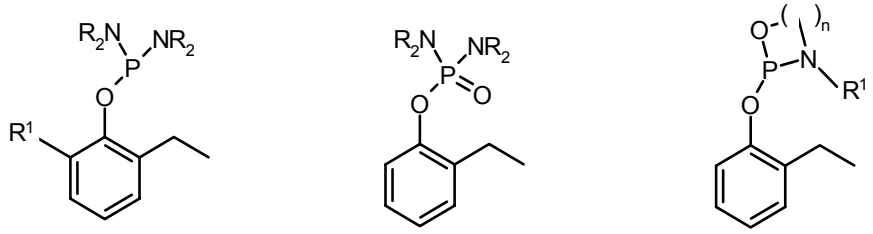
CHAPTER 3 RESULTS

3.1 NEW SYNTHETIC APPROACHES TO DIHYDROBENZOFURAN COMPOUNDS

3.1.1 DIRECTED α-METALATION APPROACH

3.1.1.1 Choice of potential DMG-s

It has already been published[49] that some phosphorous-based DMG groups facilitate regioselectively α-deprotonation (side chain)and not the *ortho*-deprotonation in the presence of *s*BuLi and TMEDA. This approach used the bis(N,N-dimethylamino)phosphoryl group as DMG (**57**). There are no published examples of compounds **86 a-c**, and **88 a-b** or their derivatives having an ethyl group in *ortho* position.[66] Within the efforts to find new DMG-s we wanted to examine other bis(N,N-dialkylamino)phosphoryl groups (**86** and **88**, Figure 11). The following compounds were chosen as model systems to examine the ratio of α- vs. *o*-deprotonation:



(**86**) R^1 = H (**87**) R^1 = OMe

a = Me
b = Et
c = *i*Pr

(**88**) **a** R = Et
b R = *i*Pr

(**57a**) R = Me

(**89**) R = *t*Bu

Figure 11. Model systems for examination of the deprotonation regioselectivity

For R^1 = H, these molecules have two potential deprotonation sites: the *ortho* position in the ring and the α-position (benzylic) in the side chain. With type compounds **86**, **87** and **88** as a substrate in metalation reaction, it would be possible to estimate influence of alkyl rest in each type of DMG-s on the regioselectivity of the deprotonation. The expected comparison of metalation products from compounds **86**, **87** and **88** would provide a qualitative picture about the influence of the phosphorous lone pair electrons from **86**, **87** and of the oxygen lone pairs from **88** on the stabilisation of the intermediate lithiumorganyls.

The regioselectivity in metalation reactions for each DMG reflects the stabilisation of the lithiumorganyls by these electron pairs. If deprotonation of **86**, **87** takes place at the aromatic nucleus, stabilisation of the lithiumorganyl requires the formation of a 5-membered ring (**91**), whereas in the case of deprotonation in the α-position, a 6-membered ring (**90**) would be formed (Figure 12). For compound **88** as the substrate, the two possible deprotonation sites invoke discrimination between a 6-membered ring (*ortho* deprotonation, **52**) and a 7-membered ring (α-deprotonation, **53**) (Figure 12). Furthermore, in this case, a lone pair from oxygen should stabilise lithium organyl making a qualitative difference compared to compounds of type **86** or **87**. Compound **89** has phosphorous incorporated in the ring structure. The rigidity of this DMG is higher than in open structures (**86**, **87** **88** and **57a**). This could have not only qualitative (regioselectivity) and quantitative (yield) effects on the reaction, but could also have an effect on the stability of compound **89**.

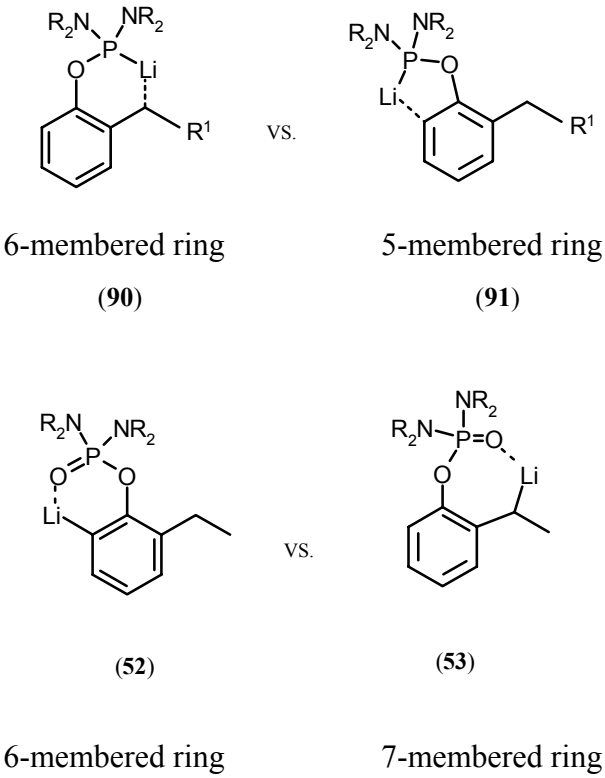
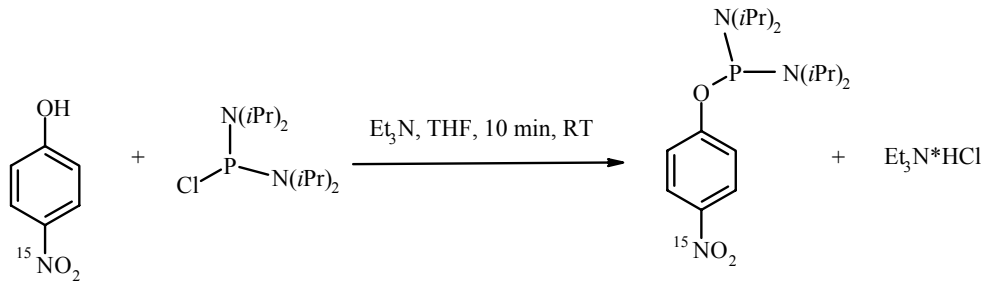


Figure 12. Possible intermediate structures in the deprotonation of **86**, **87** and **88**

It has already been described in the literature[67] that compound **94** was synthesised from bis(N,N-diisopropylamino)chlorophosphine (**93**) and phenol (**92**) (Scheme 28):

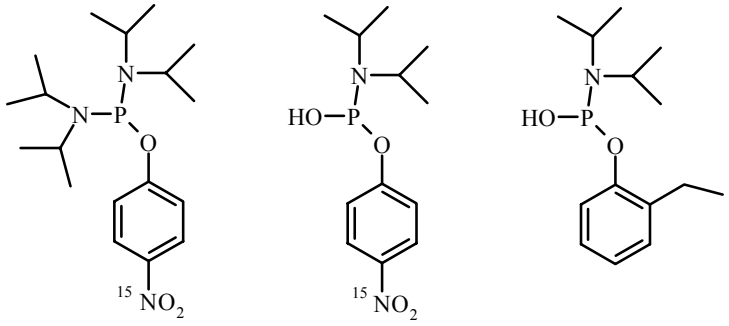


(**92**) (**93**) (**94**) (**95**)

Scheme 28. Published synthetic approach to **94**

However, in the published article the ratio of integrals: aromatic protons to protons from methyl groups in isopropyl moiety is not 1:6 (4:24) as expected, but 1:3 (4:12). Therefore, it seems reasonable to conclude that the synthesised compound is actually **96** (Figure 13), having only one diisopopylamino group connected to phosphorous.

In the repeated experiment performed under the identical reaction conditions, but using 2-ethylphenol (**105**) instead of *p*-nitrophenol, compound **97** was isolated. This result confirms our speculation that the compound, that has been isolated, had the structure **96** (Figure 13).



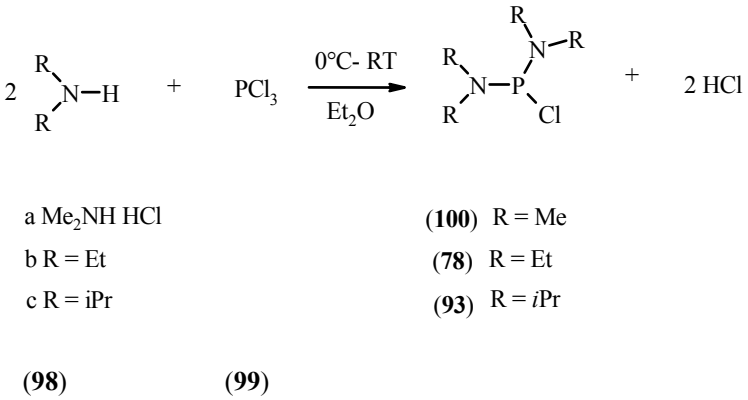
(**94**) (**96**) (**97**)

Figure 13. Published (**94**) and corrected (**97**, **96**) structures

2.1.1.2 Preparation of bis(N,N-dialkylamino) chlorophosphines

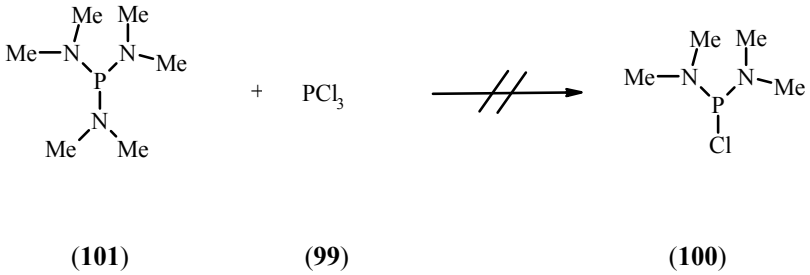
In order to synthesise compounds of type $(R_2N)_2PCl$, reactions of PCl_3 (**99**) with dialkylamines (**98 a-c**)[68] or hexamethyl phosphoroustriamine[69] (**101**) were considered as

possible approaches (Scheme 29, 30). The approach to bis(N,N-dialkyl)chlorophosphines, starting from PCl_3 and appropriate dialkylamine (dimethylamine hydrochloride was used since dimethylamine is a gas), gave satisfactory results at 0°C only for bis(N,N-diisopropyl)chlorophosphine. These reaction conditions are not suitable for the preparation of bis(N,N-diethyl)- and bis(N,N-dimethyl)chlorophosphine. bis(N,N-diisopropylamino) chlorophosphine (**93**) prepared in this way was purified by sublimation at p=1 mbar, T=90°C. White crystals were obtained.



Scheme 29. Approach to bis(N,N-dialkylamino)chlorophosphines *via* secondary amine and PCl_3

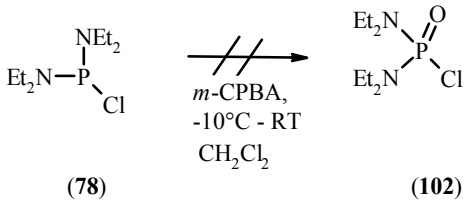
Another examined approach to $(Me_2N)_2PCl$ (**100**) was the reaction of commercially available hexamethyl phosphoroustriamine (HMPT, **101**) with PCl_3 (Scheme 30). However, the desired product could not be obtained as the pure compound.[70]



Scheme 30. Attempted approach to bis(N,N-dimethylamino)chlorophosphine (**100**) *via* HMPT and PCl_3

It has been reported that ozone (O_3) was used to prepare $(Me_2N)_2P(O)Cl$, and $(Et_2N)_2P(O)Cl$ (**102**) in 95% and 90% yield, respectively.[71]

Preparation of compound **102** was attempted using *m*-CPBA as the oxidising agent but this compound was not accessible in this way (Scheme 31) as a pure compound.

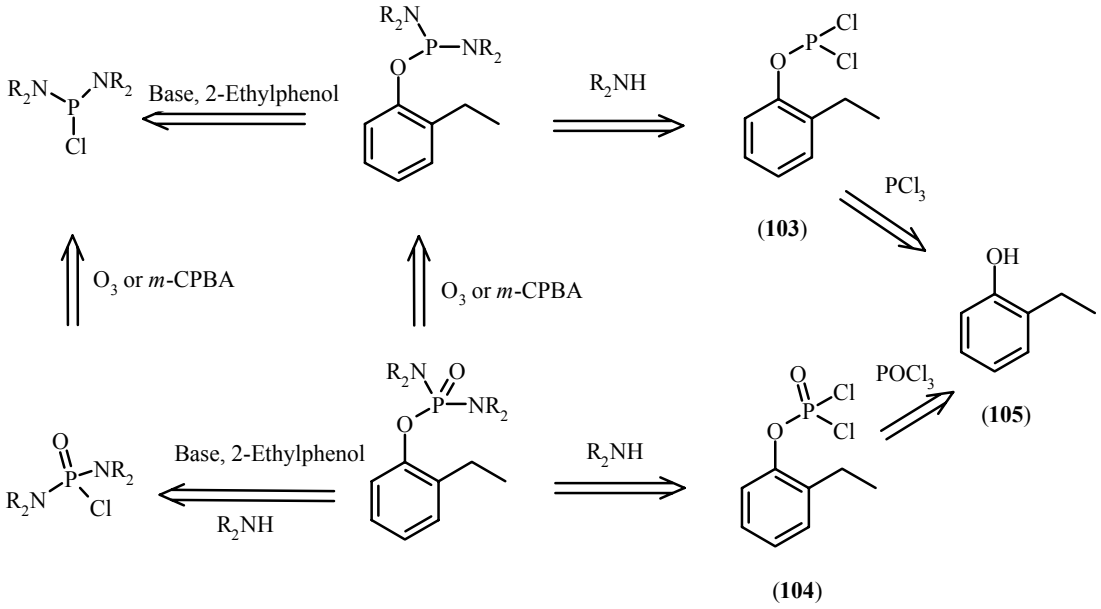


(**78**) (**102**)

Scheme 31. Possible approach to **102** *via* oxidation of **78** with *m*-CPBA

2.1.1.3 Synthesis of molecules with phosphorus DMG-s

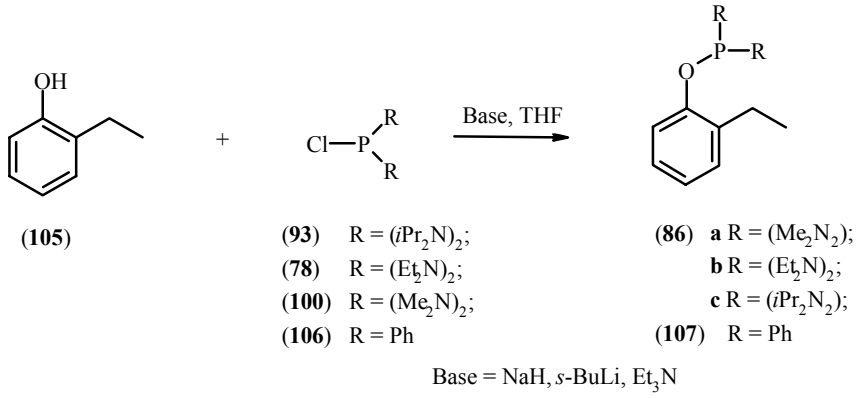
The retrosynthetic analysis for the molecules with phosphorous DMG-s leads to 2-ethylphenol as the starting material (Scheme 32):



Scheme 32. Retrosynthetic approaches to the molecules with phosphorous DMG-s

2.1.1.4 Reaction of 2-ethylphenol with bis(N,N-dialkylamino) chlorophosphines to tetraalkyl phosphoamidous acid (2-ethyl)-phenly esters

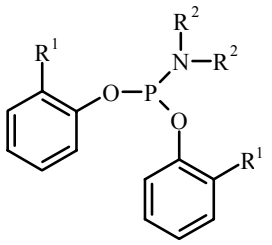
Several bases were used for the deprotonation of (**105**). Et_3N is the reagent of choice because the solid triethylammonium chloride formed during the reaction can be separated from raw reaction mixture by filtration.



Scheme 33. General approach to compounds **86** and **107** *via* reaction of 2-ethylphenol (**105**)

Surprisingly, NaH and *s*BuLi are not suitable bases for this reaction. In the case of Et_3N, base should be used in excess (4 to 20 eq). Best results were obtained using 20 eq of Et_3N with $(iPr_2N)_2Cl$, but the purification presented the major problem. Every attempt to separate desired products from side products and excess base failed: phosphoramidite decomposed quantitatively to compound **97** (Figure 13) during flash chromatography on silica gel or Al_2O_3 (with and without added base (Et_3N) to the eluent mixture).

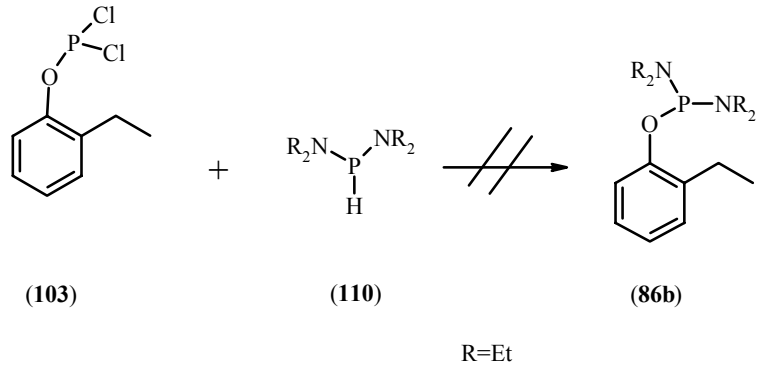
Major side products encountered in the approach that has been chosen were compounds of type **108** and **109** formed after the leaving of one dialkylamino group from the initially formed product after nucleophilic attacks of a second phenolic anion (Figure 14). Similar behaviour of the dialkylamino groups have been observed by other authors.[54-63] The integral ratio for methylene- and methyl groups from diethylamino group and aromatic side chain is 1:1, which proves that double substitution has taken place. The compound **108** was isolated in the amount that was sufficient for NMR and MS identification, but due to similar polarity with **97,** pure **108** could not be isolated.



(**108**) R^1 = Et, R^2 = *i*Pr
(**109**) R^1 = OMe R^2 = Et

Figure 14. Side product formed after double nucleophilic attack of phenol derivative **105**

Preparation of **86b** was tried with a modified procedure[72] for the preparation of phosphorodiamidous acid bis(diethylamid) phenyl ester. However, the pure compound **86b** could not be obtained.

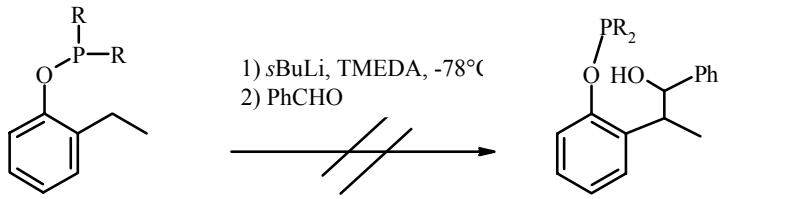


(**103**) (**110**) (**86b**)

R=Et

Scheme 34. Attempted preparation of **86 b**

Although compounds **86a, 86b,** and **86c** proved to be rather instable, raw compounds were separated from the reaction mixture by filtration from triethylammonium chloride and a metallation reaction with 1,2 eq *s*BuLi/TMEDA was performed, followed by addition of benzaldehyde to the reaction mixture. This metalation reaction was also examined on **107**. None of the compounds **111 a-d** (Scheme 35) could be detected in the NMR of the crude reaction mixture, suggesting that, desired addition of metalorganyls to benzaldehyde did not take place under these conditions.



(**86**) **a** R = $(Me_2N)_2$;
b R = $(Et_2N)_2$;
c R = $(iPr_2N)_2$;
(**107**) R = Ph

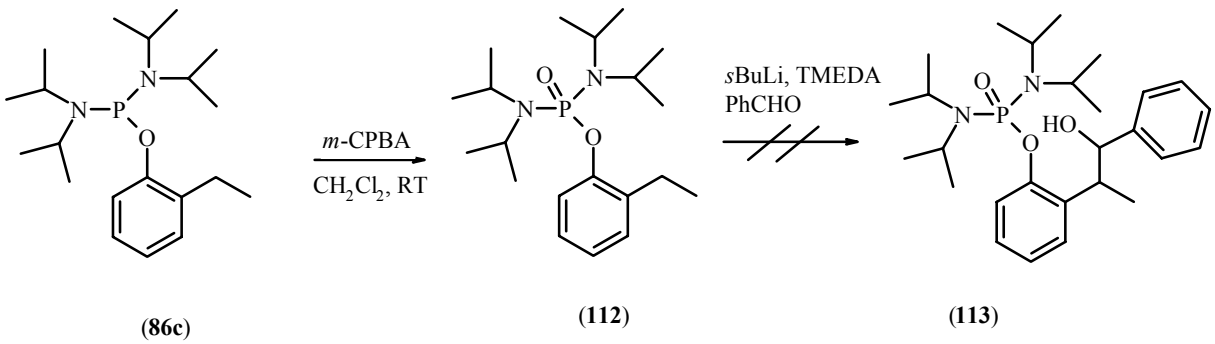
(**111**) **a** R = $(iPr_2N)_2$;
b R = $(Et_2N)_2$;
c R = $(Me_2N)_2$;
d R = Ph

Scheme 35. Unsuccessful metalation of raw, unpurified **86, 107**

3.1.1.5 Reaction of 2-ethylphenol to tetraalkyl phosphoroamidic acid (2-ethyl)-phenyl ester

It seems that the lability of the P–N bond in compound **86** (Scheme 35) represents a serious problem, and not the low valent phosphorous P(III). This lability seems to be even more pronounced with increasing sterical bulk of alkyl substituents. In order to overcome the purification problem with compound **86c**, *m*-CPBA was added directly to the reaction mixture to perform *in situ* oxidation, forming tetraisopropyl phosphorodiamidic acid (2-ethyl)-phenyl ester (phosphamidate) **112** in 40 % overall yield (Scheme 36).

Metallation of **112** with *s*BuLi/TMEDA at –105°C, and addition of benzaldehyde to the reaction mixture at -78° did not lead to **113,** which was expected to be formed from nucleophilic addition of anionic species to carbonyl group of benzaldehyde.



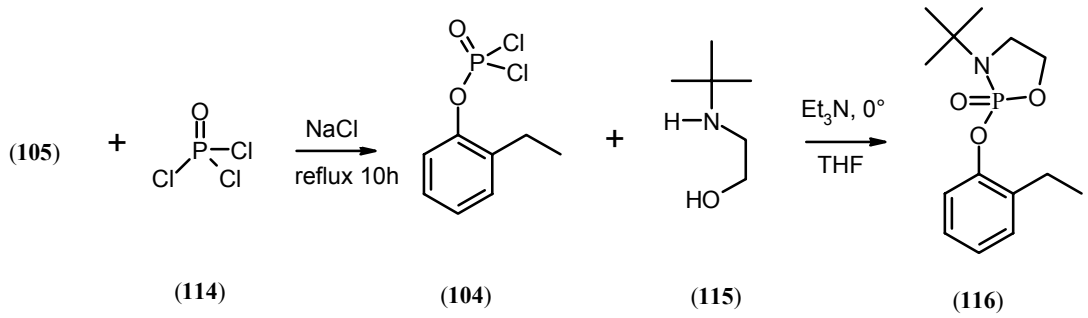
(**86c**) (**112**) (**113**)

Scheme 36. *In situ* oxidation of **86 c** with *m*-CPBA to **112**

In situ oxidation with *m*-CPBA was also studied on compound **86b** which has ethyl groups instead of isopropyl groups. However, in this case the isolated product had two phenolic moieties attached to the phosphorous according to the NMR and MS data of the crude reaction mixture.

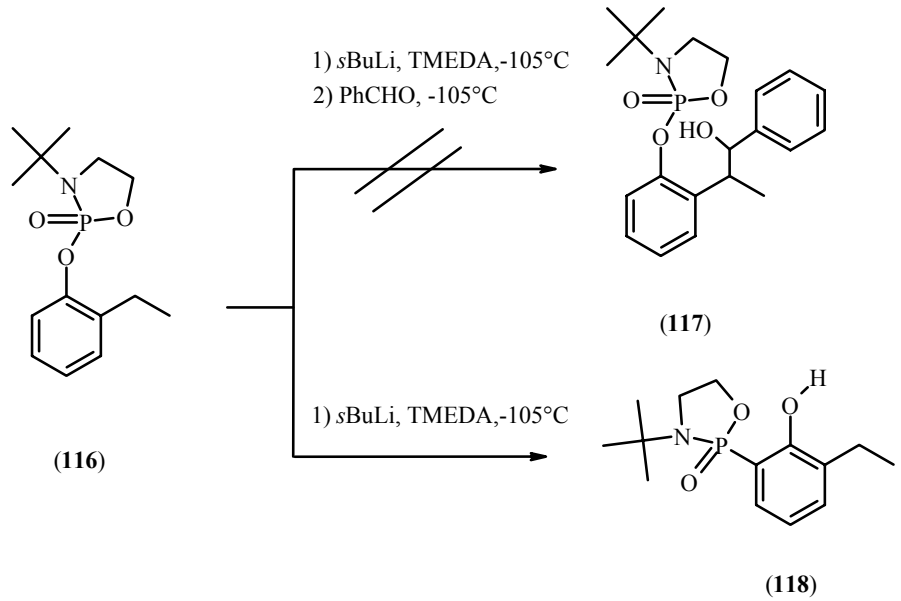
In order to study the behaviour of P(V) incorporated in a ring system, 1,3,2-Oxaphospholidine-2-phenoxy-2-oxide (**116**) (Scheme 37) was synthesised. This compound has one nitrogen and one oxygen atom connected to phosphorous. The presence of an oxygen atom, with different electronegativity and two lone electron pairs, distinguishes this molecule from phosphoamidates used so far in this research. Besides, the phosphorous atom in **116** is a part of a 5-membered ring so that sterical factors play a different role than in

acyclic derivatives. The synthesis of this compound was achieved in 25 % yield starting from 2-ethylphenol (**74**) following a modified published procedure.[73]



Scheme 37. Synthetic approach to **116** from 2-ethylphenol (**105**)

Metallation of **116** with *s*BuLi / TMEDA at −105°C and subsequent addition of benzaldehyde to the reaction mixture at −105°C did not result in the formation of the desired product (Scheme 38). The compound **118**, formed after rearrangement of **116**, was actually obtained (Scheme 38):



Scheme 38. Unsuccsessful metalation-adition sequence starting with compound **116** and formation of **118** after rearrangement

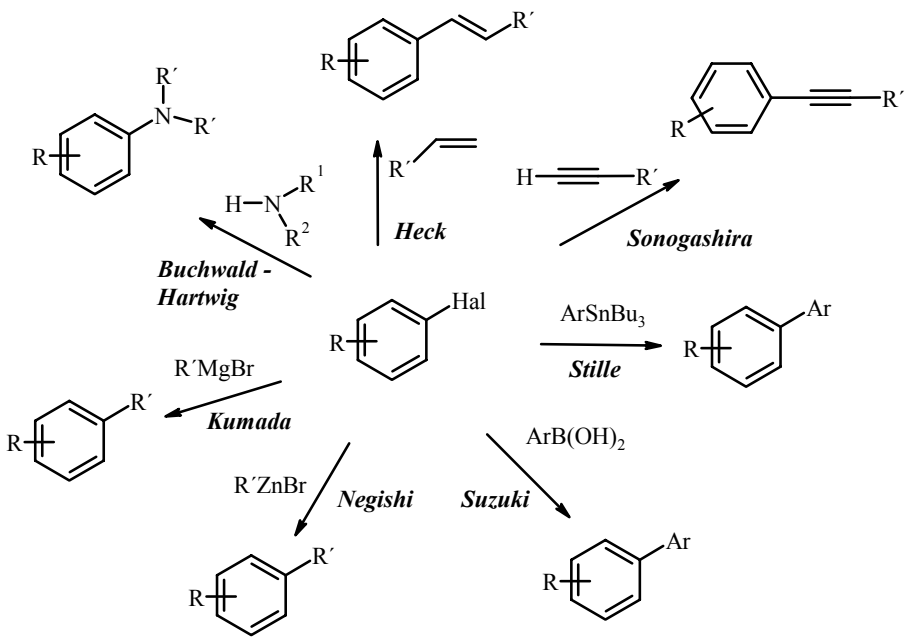
3.1.2 TRANSITION METAL CATALYSED CYCLOADDITION APPROACH

3.1.2.1 Overview

3.1.2.1.1 Cross coupling reaction catalysed by palladium

The approach that uses the same principle as nature (coupling of two molecules to yield dihydrobenzofuran moiety in one step), requires a "trick" to overcome the absence of an enzyme: the difference between the two substrate molecules has to be large enough to suppress undesired reaction pathways. The idea that the transition metal catalysts could facilitate cyclisation to dihydrobenzofurans and that the use of chiral ligands should allow control of the stereochemical outcome of the reaction was examined and is described in the next chapters of this work.

Transition metal catalysed reactions have become a very powerful tool in the arsenal of the organic chemist. Examples of some of the most important cross-coupling reactions catalysed by palladium are presented in Scheme 39:



Scheme 39. Some important palladium catalysed cross-coupling reactions

3.1.2.1.2 The Heck reaction

The Pd (0) catalysed vinylation of aryl halides was first reported in the early 1970´s in the independent studies by Mizoroki and Heck.[74] The reaction can be catalysed by palladium species, with or without phosphine ligands (phosphine assisted vs. phosphine free conditions). The role of the ligands is to form complexes with Pd(0) species, thus stabilising the actual catalyst – zerovalent Palladium.

In the first years after the discovery, the full synthetic potential of this new reaction was unappreciated and remained unused until the late 1980´s. Shibazaki[75] and Overman[76] published the first examples of asymmetric Heck reactions in 1989. The Heck reaction emerged in the last few years as a reliable method for enantioselective carbon-carbon bond formation.[77] The reaction presents one of the simplest ways to obtain variously substituted alkenes and other unsaturated compounds. Heck reactions have also been successfully used for the synthesis of tertiary and quaternary carbon centres. [108]

The enantioselective Heck reaction was reported using microwave heating that increased reaction speed and reduced the need for inert atmosphere since the reaction times were shortened from days to hours. In some cases high enantiomeric excesses were obtained (88 - 92% ee) using a thermostabile palladium-phosphineoxazoline catalytic system.[78]

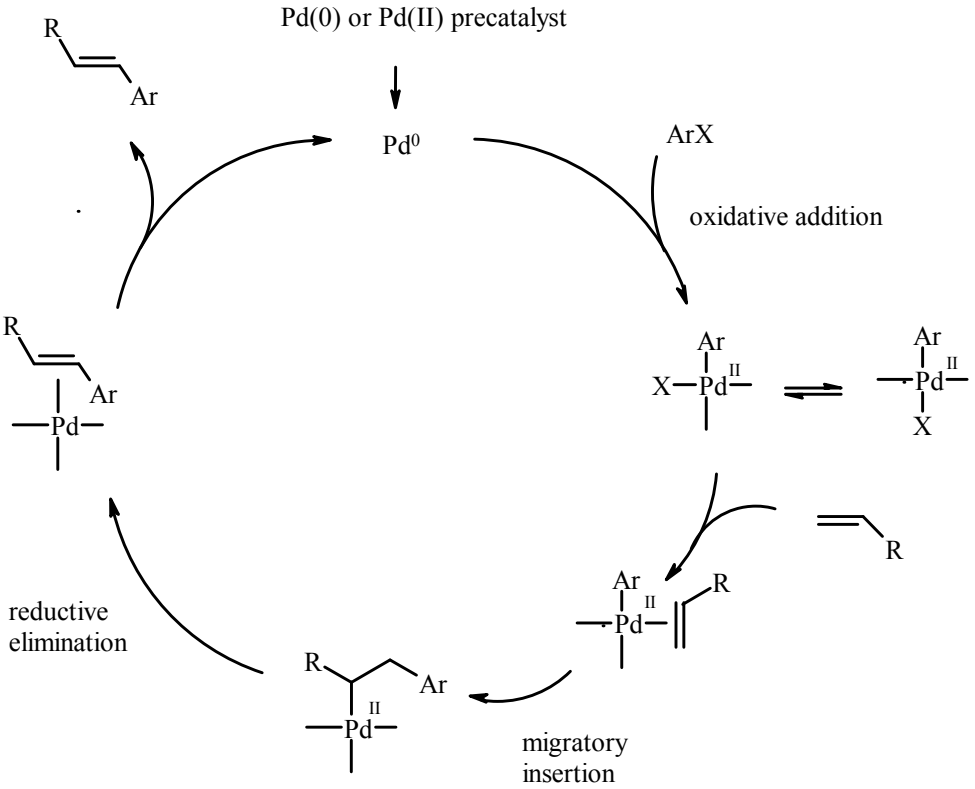
Although the Heck reaction is very attractive for industrial applications, the synthesis of an intermediate of the Prosulfuron sulfonyl urea is one of the rare examples of homogenous Heck reaction applied in industry.[79] Price of palladium is also important.

Various Pd salts and complexes can be used as palladium sources: $PdCl_2$, $Pd(OAc)_2$, $Pd(dba)_2$, $Pd_2(dba)_3{\cdot}CHCl_3$, $Pd(PPh_3)Cl_2$, etc. Under the reaction conditions, Pd(II) compounds are reduced to Pd(0) species which are considered to be the actual catalytic species.

Typical solvents for the Heck reaction are DMF, NMP, toluene or acetonitrile. It was recently reported that poly(ethylene)glycol (PEG), having a molecular weight of 2000 (or lower) has been used as an efficient reaction medium for the Heck reaction.[80] Using this approach, the catalyst and solvent can be reused.

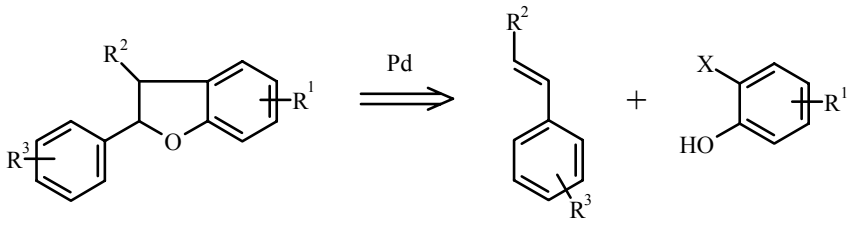
The Heck reaction may proceed *via* several reaction pathways similar to the "textbook" mechanism, since the attacking species and substrates could be diverse. This classical mechanism (Scheme 40) has been questioned[81] since it is not in agreement with some important experimental observations. For example, a pronounced influence of the counterions of the palladium(II) precatalysts and added metal salts on the catalytic activity

was often observed,[82] although they do not appear in the general mechanism for the Heck reaction (Scheme 40).



Scheme 40. Simplified "textbook"mechanism of the Heck reaction

From the reactions in Scheme 39, the Heck reaction seems to be the most promising candidate for the synthetic approach to dihydrobenzofurans. A retrosynthetic scheme based on one modification of the Heck reaction (the Heck oxyarylation reaction) is shown in Scheme 41:

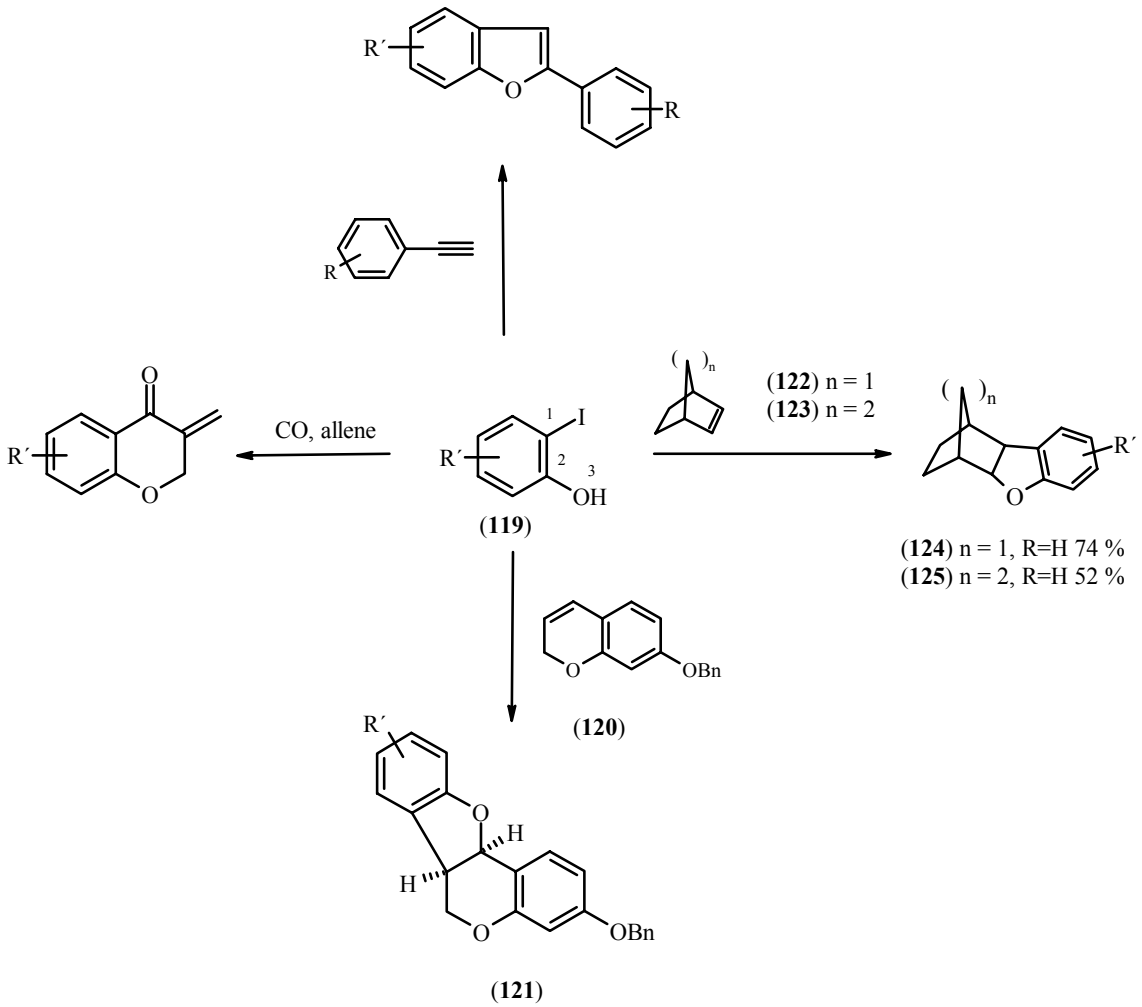


Scheme 41. Dihydrobenzofurans *via* Heck oxyarylation reaction

3.1.2.1.2 The Heck oxyarylation reaction

The oxyarylation reaction can be regarded as pseudo [3+2] cycloaddition; some examples with *ortho*-iodophenol derivatives and allenes, alkines or alkene derivatives are displayed in Scheme 42. The Heck oxyarylation reaction involves an aryl-palladium species with activated aromatic carbon and oxygen from the phenol group in positions 1 and 3 (**119**, Scheme 42), and two neighbouring carbons from the double bond.

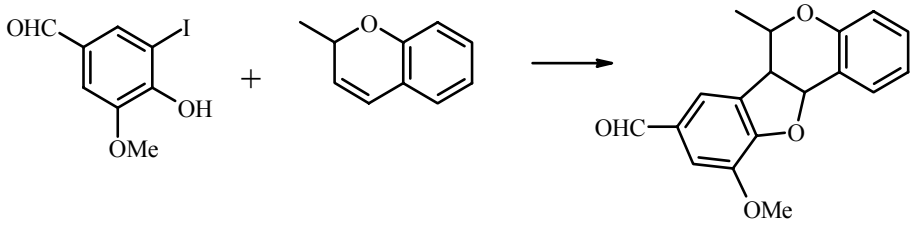
The Heck oxyarylation reaction is an intermolecular sp^2–sp^2 coupling reaction catalysed by palladium. Some intramolecular sp^2–sp^2 coupling rections have been described in the literature.[83] Compounds containing *cis*-dihydrobenzofuran moiety of pterocarpans (**121,** R=H) were synthesised by the palladium catalysed annulation of 1,3-dienes and *o*-iodophenols as early as 1990:[84]



Scheme 42. Oxyarylation reactions with *ortho*-halogenphenols

Studies with *o*-iodophenol as the starting material for the Heck oxyarylation reaction showed that some unidentified tarry side products were formed, decreasing the yield of the desired product.[85] Derivatives of vanilline having one methoxy group and one aldehyde group at the appropriate positions in the aryl moiety, were considered as the starting material for the oxyarylation reaction because some natural 8,5'-neolignans have also one methoxy group and a side chain attached to the aromatic moiety of the dihydrobenzofuran core.

Iodovanilline (**126**) has already been used as a substrate in the annulation reaction[86] with benzopyran (**127**) (Scheme 43). The double bond participating in the reaction was a part of a cyclic system; the yield of *cis*-pterocarpan (**128**) was modest (34 %).



(**126**) (**127**) (**128**)

Scheme 43. Annulation reaction of iodovanilline with **127** to form *cis*-pterocarpan **128**

Although the approach to dihydrobenzofurans *via* the Heck oxyarylation reaction seems straightforward, several side reactions, noticed during the studies of similar reactions, have been reported:

1) Decomposition of the soluble catalyst, (precipitation of the palladium metal):
Two possible explanations[87] for the deposition of palladium metal are the reaction of the ligand (Ph_3P) leaving weakly solvated palladium atoms, which rapidly formed insoluble metal, and dissociation of the palladium(0)-phosphine intermediate under the reaction conditions leading to agglomeration of weakly complexed Pd atoms (e.g. $S_3Pd(Ph_3P)$ or $S_2Pd(Ph_3P)_2$, S= solvent) to form the metal.

2) Formation of diaryl ethers:
Diaryl ethers have been obtained by the reaction of arylpalladium halides with sodium aryloxides.[88]

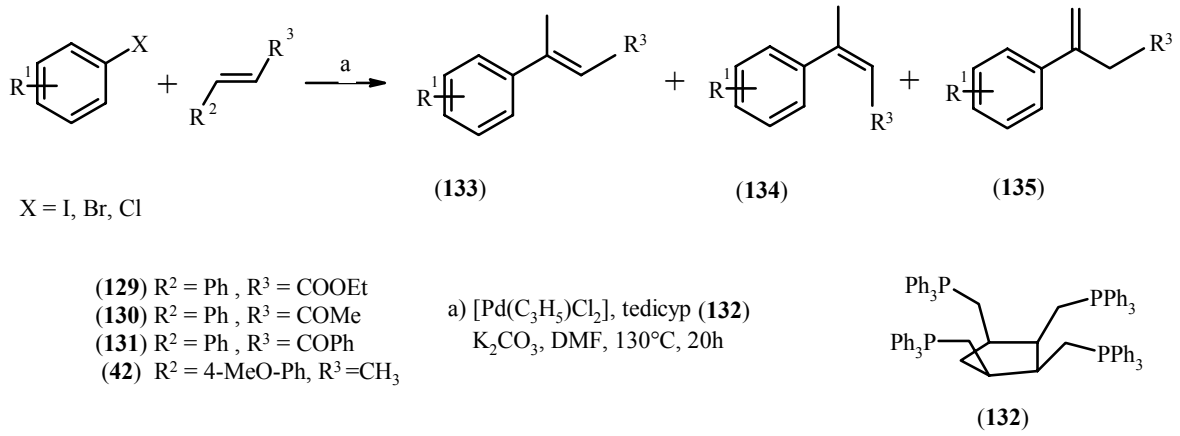
3) Reaction between Pd(0) and Ag(I):

A redox reaction between the palladium(0) catalyst and silver(I) cation was proposed[89] in order to explain lower yields and the observed mirror on the reaction vials.

$$Pd(0) + 2Ag(I) \rightarrow 2Ag(0) + Pd(II)$$

3.1.2.1.4 The Heck reaction of vicinal 1,2-disubstituted alkenes

The Heck reaction with non-cyclic, vicinal disubstituted alkenes has attracted less attention and is much less studied than the reaction of monosubstituted (terminal) alkenes. Santelli *et al.* [90] showed that the tetraphosphine ligand Tedicyp (**132**) and $[Pd(C_3H_5)_2Cl]_2$ catalysed the Heck reaction of 1,2-disubstitutied alkenes such as E-ethyl cinnamate, E-benzalacetone, E-benzalacetophenone and E-anethole.



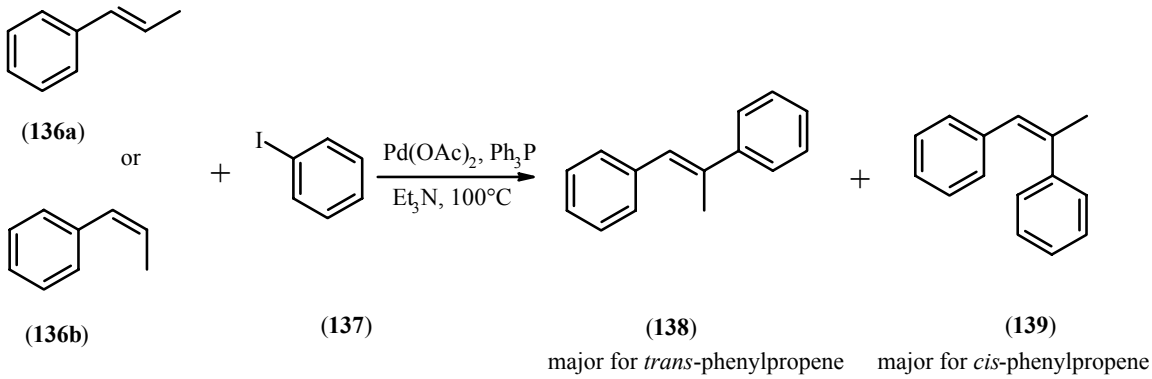
Scheme 44. Heck reaction of 1,2-disubstituted alkenes with halogenaryls catalysed by palladium

The Heck reaction with anethole (**42**) was performed with 4-bromoanisole and gave a mixture of compounds **133**, **134**, and **135** in 75 % yield and ration 1:1:1.

The selectivity of the reaction was found to be dependent on the substituents of the alkenes, yielding mixtures of isomeric products. The observed lack of selectivity was explained by equilibration of the product subsequent to the Heck reaction by a base-catalysed isomerisation.[91]

The influence of the double bond stereochemistry[92] on the stereochemistry of the products was studied in the reactions of *trans*- and *cis*-1-phenyl-1-propenes (**136a, b**) with phenyliodide (**137**) (Scheme 45).

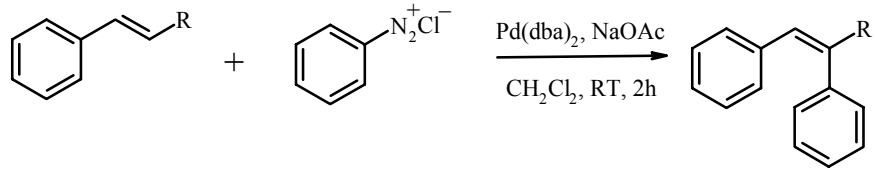
Yields of up to 99% were obtained: *trans*-phenylpropene (**136a**) gave predominately *trans*-1,2-diphenyl-1-propene (**138**), and *cis*-phenylpropene (**136b**) gave *cis*-1,2-diphenyl-1-propene (**139**) as the major product. Reactions were performed with and without Ph_3P (2 eq) as the ligand.



(**136a**) *trans*-phenylpropene
(**136b**) *cis*-phenylpropene

Scheme 45. Influence of double bond geometry of (**136**) on the product distrubution in reaction with PhI (**137**)

Diazonium salts were also used as the substrates in the Heck-reaction. A nice illustration about the influence of the alkene starting material was showen in a study by Kikukawa *et al.*[93] (Scheme 46). With styrene (**140**) terminal alkene as a starting material, the yield of the Heck product **142** was 51 %, whereas with phenylpropene (**136a**) (internal alkene) under the same reaction conditions compound **143** was formed in only 6 % yield. This high difference in yields points out the importance of substituents on the double bond. The actual cause for the low yield in the case of phenylpropene was not previously further investigated.



(**140**) R = H
(**136 a**) R = Me

(**141**)

(**142**) R= H 51 % yield
(**143**) R = Me 6 % yield

Scheme 46. Influence on substitution pattern of alkene on the yield of the Heck product with diazonium salt

3.1.2.2. Synthetic approach to dihydrobenzofurans via palladium catalysed cycloaddition reaction of halogen phenols

Enzymes, as postulated, control the biosynthesis of dihydrobenzofuran neolignans in nature, by enabling the coupling of two molecules of phenylpropene derivatives (sinapic, coumaric and ferulic alcohol, or similar derivatives with different functional group attached to the double bond).[108]

In the active centre of the enzyme two molecules are oriented in a way that the quinone methide intermediate formed from one molecule can add in radical fashion to the double bond of another molecule, thus enabling ring closure to the dihydrobenzofuran system.

Transition metal catalysed cycloaddition reactions are suitable candidates for the equivalent synthetic procedure that enables ring closure in one step, with the possibility of controlling the stereochemical outcome of the reaction by the transfer of chirality from the chiral ligands employed. Pd, Pt and Ni were considered as possible candidates for a transition metal catalyst. Up to now, only Pd was able to catalyse this reaction.

As it was shown in Scheme 45, the stereochemistry of the alkene double bond has a strong influence on the distribution of the products from the Heck reaction between aryl iodide and phenylpropene. In the oxyarylation reaction, the aryl starting material is more complex than the simple halogenoarene, leading to a more complex reaction pathway. It seems reasonable to expect that the stereochemistry of the alkene double bond would also have a significant, if not crucial, influence on the regio- and stereochemichtry of the products from the Heck oxyarylation reaction.

To the best of our knowledge, ring-closing reactions have not been examined on open chain phenylpropenes having *trans*- or *cis*-configuration of the double bond. A very interesting question of what impact the geometry of the double bond has on product distribution and regio- and stereochemistry of dihydrobenzofuran products (Figure 15) was addressed in this dissertation.

Heck oxyarylations being performed on double bonds that are part of a ring system (*cis*-configuration of the double bond) have a consequence that only *syn*-"addition" of halogenophenol to the alkene is possible. Heck oxyarylation reactions have not been performed on the internal double bond of phenylpropenes. When the double bond is not a part of the ring system, there is a possibility of the free rotation around C–C bond before the reductive elimination of the palladium intermediate (Scheme 52). The question of the

stereochemical outcome of the reaction is raised while the dihydrobenzofuran product can be formed as *cis*- and/or *trans*-diastereomers (Figure 15).

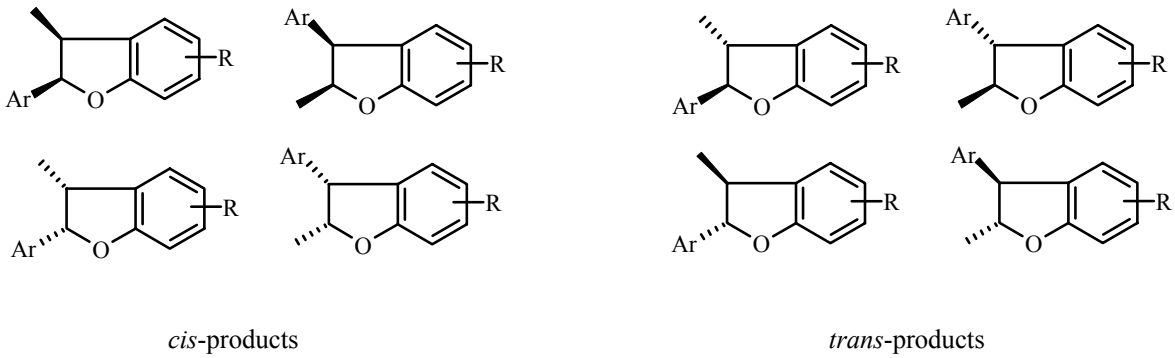


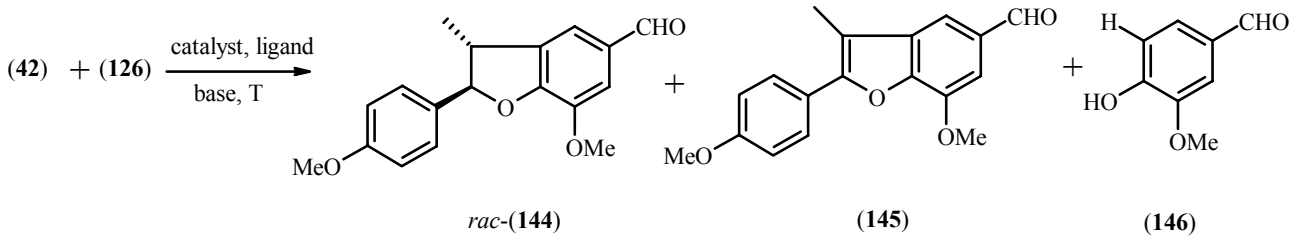
Figure 15. Eight possible dihydrobenzofuran isomers that can be formed in the palladium catalysed ring-closing reaction

During the present project development, a study was published showing that phenylpropenes with *cis*-configuration of the double bond can isomerise to the *trans*-isomers in the presence of the palladium(II)catalysts.[94] This isomerisation of the double bond conjugated to aromatic systems represents an attractive general method for preparation of pure *trans*-isomers due to the mild reaction conditions.

3.1.2.2.1 Anethole as the starting material in the Heck oxyarylation reaction

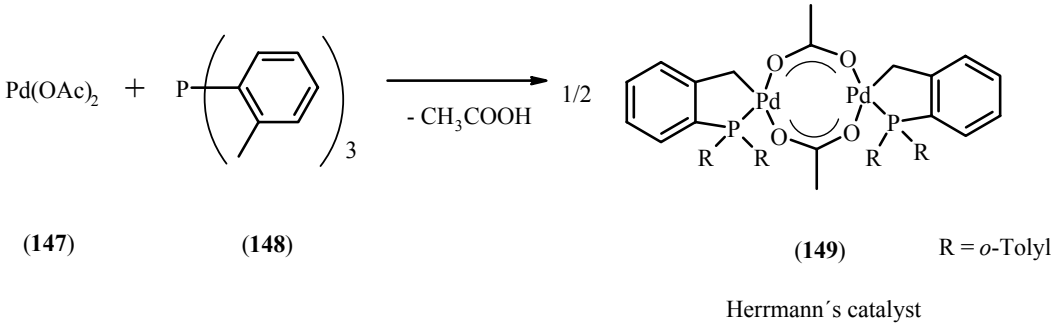
In the approach to dihydrobenzofuran-type neolignans *via* palladium-catalysed reaction, the reaction between anethole (**42**) and iodovanilline (**126**) was chosen to be the model system (Scheme 47):

The iodovanilline (**126**) was chosen as the starting material because the *p*-formyl group allows a convenient extention of the side chain, activates the phenolic hydroxy group, and is, according to literature, inert in palladium catalysed reactions. Beside the dihydrobenzofuran product (**144**) several other side products, such as benzofuran (**145**) and vanilline (**146**) (Scheme 47), have been isolated.



Scheme 47. The desired product **144** and side products **145** and **146** in the model reaction

The reaction of Pd-catalysed cycloaddition (Scheme 47) is very dependent on the reaction conditions. The reagent of choice for a palladium source is $Pd_2(dba)_3 \cdot CHCl_3$, though $Pd(OAc)_2$ (with and without added Ph_3P), $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$ and $Pd(acac)_2$ can also catalyse the reaction. However, some palladium catalysts such as: $Pd(P(o\text{-Tol})_3)_2Cl_2$, $PdCl_2$ in the presence of the following ligands: (Ph_3P, $P(o\text{-Tol})_3$, (–)-sparteine, phenanthroline), and $Pd(OAc)_2$ in the presence of the following ligands: (–)-sparteine, phenanthroline, pyridine and Ph_3As did not give any desired product. Herrmann´s catalyst[95] (**149**) (Scheme 48) was also inactive under the reaction conditions (T>80°C).



Scheme 48. Synthesis of Herrmann's catalyst **149**

Experiments with other catalysts of transition-metals showed no reaction (e.g. $NiCl_2$ and Ph_3P, $NiCl_2$ and $P(o\text{-Tol})_3$, $Ni(dppe)Cl_2$, $Pt(PPh_3)_4$).

Dihydrobenzofurans (Scheme 47) were formed under "ligand free" conditions ($Pd(OAc)_2$ without added ligand), as well as in the presence of strong coordinating ligands: Ph_3P, $(C_6F_5)_3$ P , tBu_3P.

The choice of base (Scheme 47) is also of crucial importance, many bases such as Na_2CO_3, $NaHCO_3$, Na_2CO_3 + Bu_4NCl, $NaHCO_3$ + LiCl, NaOAc, $CaCO_3$, $CsCO_3$, $TlCO_3$,

tBuOK, $Bu_4N^+Cl^-$, amines (Et_3N, *i*Pr_2NEt, (–)-sparteine) and pyridine, typically used in transition metal catalysed reactions, failed to afford any product. For a successful cycloaddition, a silver salt must be present as a base. A set of experiments was performed with different bases under otherwise identical conditions: Ag_2CO_3 enabled successful reaction whereas Na_2CO_3, K_2CO_3, $CaCO_3$, $TlCO_3$ or Cs_2CO_3 did not. Among the bases that contain Ag^+, Ag_2CO_3 is the reagent of choice. Other silver salts, such as AgOTf, Ag_3PO_4, and AgOAc led only to formation of traces of product. Combinations of Ag_3PO_4 and Na_2CO_3 or K_2CO_3 were also unsuccessful.

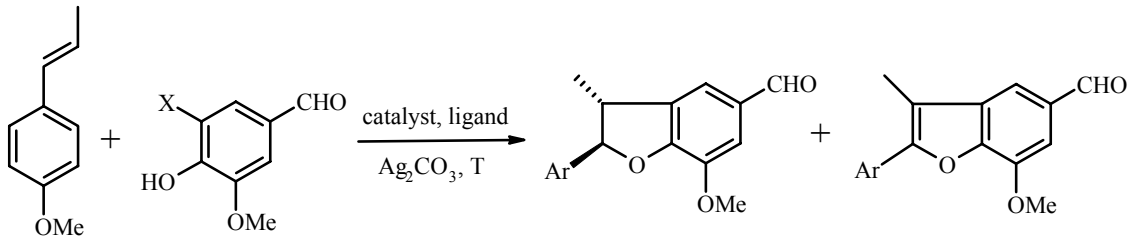
The role of Ag^+ ion is not fully elucidated. It has been proposed[96] that it forms insoluble AgI, thus making a 16-electron cationic palladium intermediate (Scheme 65). However, because of its oxidative potential, the silver ion may be responsible for the oxidation of the initially formed dihydrobenzofuran and formation of the benzofuran side product.

Tl^+ and R_4N^+ are, like Ag^+, large cations that form insoluble or tightly aggregable iodides. However, the use of $TlCO_3$ or alkylammonium halides did not result in the formation of any product. This result points out that some unique property of Ag^+ that lacks in the other two cations, probably the oxidative capability or the ability to coordinate alkenes, plays the crucial role in the reaction mechanism. Further experiments are needed.

The oxyarylation reaction can be performed in DMF, NMP, dioxane, *n*BuOH, toluene or mesitylene. The use of DMSO or CH_3CN as a solvent did not yield the product. Addition of water to the reaction mixture with DMF as a solvent (ratio DMF: H_2O up to 4:1) led to formation of the product but in lower yield and with more side products.

The alkene : palladium catalyst ratio is important, the reactions were performed with 1,2 molar excess of the alkene compound relative to the phenol derivative if not otherwise stated. It has been proposed[97] that the alkene compounds can play a role in the oxidative addition, by stocking part of the active palladium(0)species under the unreactive 18-electron complex.

The major product of this reaction is *trans*-dihydrobenzofuran (**144**), with a *cis* / *trans*- ratio of (at least) 1:10, dependent on the reaction conditions. The *trans*-diastereoselectivity is probably favoured by the higher thermodynamical stability of the *trans*-isomers compared to the *cis*-isomers. Recorded NMR COSY and NOESY spectra confirmed that the product has a *trans*-geometry. Reaction between anethole (**42**) and halovanillines is presented in Scheme 49:



(**42**) (**126**) X = I (**150**) X = Br *rac*-(**144**) (**145**)

Ar = 4-MeO-Ph

Scheme 49. The palladium catalysed reaction between anethole (**42**) and halogen vanillines **126** and **150**

Table 3. Yields and conditions for the reaction in Scheme 49

Entry	Catalyst (6 mol%)	Halogen	T[°C]	Solvent	Yield 144 / Yield 145 [%]
1	$Pd(OAc)_2$	I	50°	mesitylene	23 % (**144**)
2	$Pd_2(dba)_3 \cdot CHCl_3$	I	50°	DMF	33 % (**144**)
3	$Pd(Ph_3P)_2Cl_2$	I	80°	DMF	19% / 19%
4	$Pd(Ph_3P)_2Cl_2$	I	80°	toluene	28% / 28%
5	$Pd(Ph_3P)_2Cl_2$	Br	80°	DMF	6 % / 30%
6	$Pd(Ph_3P)_2Cl_2$	Br	120°	DMF	7 % / 35%

As can be seen in the Table 3, iodovanilline (**126**) as starting material has advantages over bromovanilline (**150**), because the reaction can be performed at lower temperature (50°C), yields of **144** are better with iodovanilline (entries 3 and 5) and less benzofuran (**145**) is formed in the course of the reaction. A review on the effects of halogens in the transition metal catalysis has been published by Fagnou and Lautens.[98]

Two experiments were performed with iodovanilline (**126**) and bromovanilline (**150**) as the starting materials (Table 3, entries 3, 5), under otherwise identical conditions: anethole, DMF, $Pd(PPh_3)_2Cl_2$, Ag_2CO_3, 80°C. In the experiment with iodovaniline (entry 3), the 1:1 mixture of benzofuran (**145**) and *trans*-dihydrobenzofuran (**144**) were formed, whereas the bromovanilline (entry 5) led predominatly to formation of the benzofuran (**145**) (ratio **144**:**145** being 1:5). Bromovanilline was reactive only at 80°C or higher temperatures.

Experiments presented in Table 4 show that the best yield was obtained from NMP as the solvent (entries 1 and 5), although the selectivity for the formation of dihydrobenzofuran and benzofuran is low (1:1 entry 1). In dioxane (entry 2) the yield was lower (21%) but the selectivity was better (2:1). The best selectivity was obtained from *n*BuOH (6:1, entry 3), but it was accompanied with the low yield of 17% **144** .

Table 4. Yields and conditions for the reaction of iodovanilline (**126**) and **42** (Scheme 49)

Entry	Catalyst	Solvent	Ligand	Ratio 144 : 145	Yield 144 [% GC]
1	$Pd(OAc)_2$	NMP	–	1 : 1	34
2	$Pd(OAc)_2$	Dioxane	–	2 : 1	21
3	$Pd(OAc)_2$	1-butanol	–	6 : 1	17
4	$Pd(OAc)_2$	NMP	–	1 : 1	41[a]
5	$Pd_2(dba)_3{\cdot}CHCl_3$	NMP	–	3 : 2	37
6	$Pd[(acac)F_6]_2$	NMP	–	1 : 2	20
7	$Pd(OAc)_2$	NMP	1 eq Ph_3P	1 : 2	22[b]
8	$Pd(OAc)_2$	NMP	2 eq Ph_3P	1 : 2	19[b]
9	$Pd(OAc)_2$	NMP	3 eq Ph_3P	2: 3	6[b]
10	$Pd_2(dba)_3{\cdot}CHCl_3$	NMP	2 eq Ph_3P	1 : 1	38[b]
11	$Pd(OAc)_2$	Dioxane	2 eq Ph_3P	1 : 1	25
12	$Pd(OAc)_2$	1-butanol	2 eq Ph_3P	2 : 1	33

Conditions: 1 eq iodovanilline, 1,2 eq. anethole, 1,2 eq. Ag_2CO_3, 5 mol% catalyst, 50°C, 24h
[a] 1,4 eq iodovanilline, 1 eq. anethole, 1,2 eq. Ag_2CO_3, 5 mol% catalyst, 50°C, 24h ; [b] reaction time 3 days

The good dihydrobenzofuran : benzofuran ratio was obtained from *n*-butanol presumably because the Ag^+ excess (in 1,2 eq Ag_2CO_3 there is 2,4 eq of Ag^+) reacted with the solvent, oxidizing it to 1-butanal. In this way, silver ions are no longer available for oxidation of dihydrobenzofuran to benzofuran.

Reactions in Table 4 were performed under the following conditions: 1 eq iodovanilline, 1,2 eq anethole, 5 mol% catalyst, 50°C, Ag_2CO_3 as a base for period of 24h if not otherwise stated. In one reaction (entry 4) the iodovanilline was used in excess (1,4 eq iodovanilline, 1 eq anethole) and the increased amount of iodovanilline resulted in increased yield of 41% **144,** compared to 34% of **144** in entry 1.

Entries 1, 5 and 6 show the influence of the catalyst over the course of the reaction: $Pd(OAc)_2$ and $Pd_2(dba)_3{\cdot}CHCl_3$ were almost equally effective (34% – 37%), with

$Pd_2(dba)_3 \cdot CHCl_3$ being more selective. $Pd[(acac)F_6]_2$ produced dihydrobenzofuran in a lower yield (20 %) and unfavourable selectivity (1:2).

Addition of the phosphine ligand (Ph_3P) to $Pd(OAc)_2$ resulted in decreased yield and a slower reaction (entries 7, 8 and 9). After 3 days in the reaction with 1 eq Ph_3P, dihydrobenzofuran **144** was formed in 22% yield. An increase of the amount of Ph_3P to 2 eq resulted in the formation of 19% of **144**, and in the reaction with 3 eq only 6 % of **144** was formed. A sharp drop of yield in the experiment with 3 eq of Ph_3P is due to the saturation of catalyst with the ligand.

$Pd_2(dba)_3 \cdot CHCl_3$ was less sensitive to added Ph_3P (entry 10) than $Pd(OAc)_2$. The addition of 2 eq Ph_3P gave **144** and **145** with no preference. This experiment shows that Ph_3P doesn't play such an important role with $Pd_2(dba)_3 \cdot CHCl_3$ as the palladium source as it does with $Pd(OAc)_2$. The reason for this could be the dibenzylideneacetone ligand (dba), which remains coordinated to palladium species during the reaction, thus diminishing the role of the phosphine ligand. Amatore and Jutand have shown that 10 eq of Ph_3P are necessary for complete displacement of dba from the palladium.[(99)] The reactions shown in entries 11 and 12 have been performed with $Pd(OAc)_2$ and 2 eq Ph_3P in dioxane and *n*BuOH. Compared with the ligand-free reactions (entries 2,3), the selectivity was decreased in the presence of phosphine ligands, but the yield of dihydrobenzofuran increased from 21% to 25% in dioxane and from 17% to 33% in n-butanol.

The influence of the solvent can be seen in the following example: change from DMF to less polar 1,4-dioxane leads to change in the distribution of products. The best selectivity between the formation of dihydrobenzofuran and benzofuran was achieved in 1-butanol (entry 3).

Beside the compounds (**126**) and (**150**) several other *o*-halo-phenols were prepared and tested as starting materials (Figure 16). The carbonyl group of **126** was reduced to alcohol **151**. The compound **151** was not suitable for this reaction since the dihydrobenzofuran product was not formed. The alcohol group of **151** was oxidized to aldehyde group under the reaction conditions, yielding compound **126.** The carbonyl group of **126** and **150** was protected with 2,2-dimethylpropandiol as acetal, according to a published procedure,[(100)] yielding compounds **152** and **154.** With these compounds as the starting materials, the formation of any product was not observed. Transformation of the aldehyde group of **126** and **150** to a propene side chain was accomplished in a Grignard reaction with EtMgBr, followed by water elimination with anhydrous $CuSO_4$ providing **153**.

Compound **153** was not a suitable starting material for the oxyarylation reaction; it did not lead to formation of any product.

These results clearly show that the electron pulling aldehyde group in *para*-position to phenolic hydroxyl group plays a very important role in this reaction.

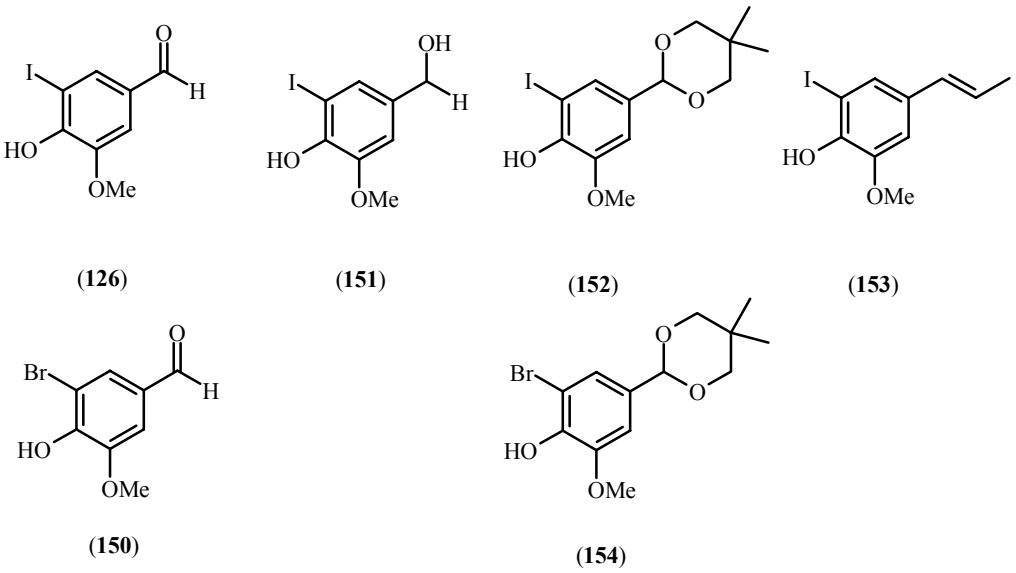


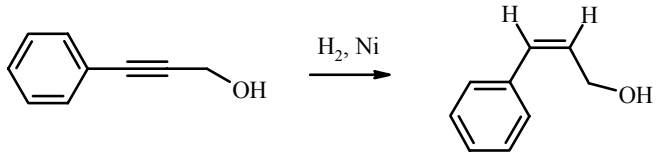
Figure 16. Several derivatives of compounds **126** and **150** studied in the palladium catalysed reactions

One of the possible problems in the reactions of halogenophenols with palladium compounds is chemoselectivity: halogenophenols have two possible reactive sites (–OH and Ar–X) that can react with palladium catalyst under the reaction conditions. Depending on the nature of the halogen, more accurately on the oxidative addition step, either of the two possible reaction pathways can prevail. In the case of aryliodides, the oxidative addition takes place first. The problem of chemoselectivity in the *ortho*-halogenophenols has been addressed in earlier work[101] with bromophenol and norbornadiene, where it has been shown that phenolic –OH reacts with Pd catalyst before the oxidative addition into the aryl-halogen bond takes place. The reaction pathway where oxidative addition takes place first gave minor product.

3.1.2.2.2 Cinnamic alcohol as the starting material in the Heck oxyarylation reaction

In order to investigate the scope of the oxyarylation reaction, cinnamic alcohol was employed as the starting material.

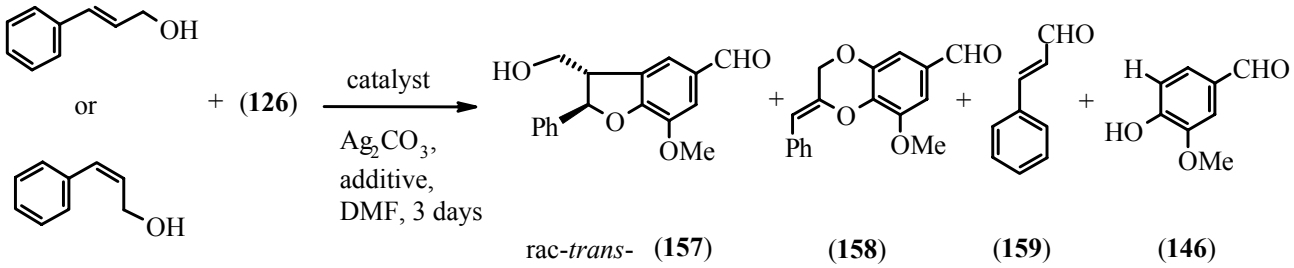
Trans-cinnamic alcohol (*trans*-156) is commercially available; *cis*-cinnamic alcohol (**156**) was prepared by hydrogenation of 1-phenyl-1-propin-3-ol (**155)** according to the published procedure[102] (Scheme 50):



(**155**) *cis*-(**156**)

Scheme 50. Preparation of *cis*-cinnamic alcohol (**156**)

In the Heck oxyarylation reaction of *trans*- and/or *cis*-cinnamic alcohol (**156**) and iodovanilline (**126**) in DMF (Scheme 51), the desired product **157** together with several side products are formed: benzodioxine (**158**) is formed by cross coupling, cinnamic alcohol is oxidised to cinnamic aldehyde (**159**) and iodovanilline is reduced to vanilline (**146**).



trans- or *cis*- (**156**) rac-*trans*- (**157**) (**158**) (**159**) (**146**)

Scheme 51. Palladium catalysed reaction between cinnamic alcohol (**156**) and iodovanilline (**126**)

Table 5. Influence of the reaction conditions on the ratio of the products from Scheme 51

Entry	Load [mol %]	Catalyst	Double bond geometry	T[°C]	Yield 157 [%]	Ratio 157 : 158 : 159		
1	6	$Pd(OAc)_2$	*trans*	50°	32	10	1	4
2	6	$Pd(PPh_3)_2Cl_2$	*trans*	50°	42	28	1	35
3	6	$Pd(OAc)_2$	*cis*	50°	31	1	1	0,1
4	10	$Pd(PPh_3)_2Cl_2$	*trans*	80°	40	1	1	0,3
5	10	$Pd(OAc)_2$	*trans*	80°	37	2	1	0,2
6	10	$Pd(OAc)_2$	*trans*	80°	29[a]	2	1	1

[a] H_2O was added to the solvent, ratio DMF:H_2O = 3:1

The reactions, performed in the presence of amine bases, did not yield any product and cinnamic aldehyde formation was not observed.

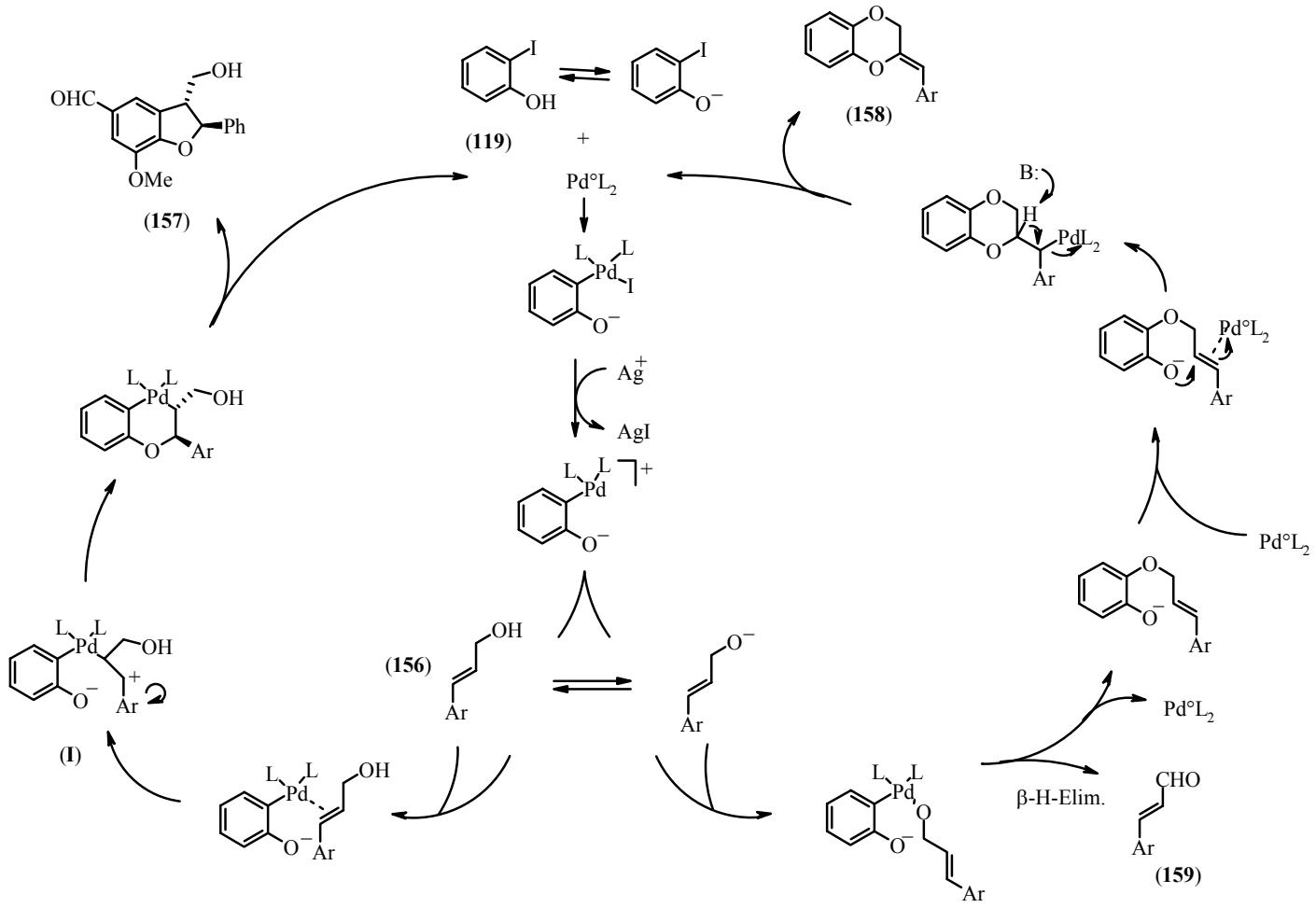
As it can be seen in the Table 5, a temperature increase from 50°C to 80°C did not improve the yield of **157** significantly, but increased the formation of side products. These not fully characterised side products show characteristic signals for the aldehyde group in the NMR spectrum of the crude reaction mixture. Both *cis*- and *trans*-**156** gave *trans*-**157** in comparable yield. In the experiment with *cis*-**156** the side product was formed in a higher amount than in experiment with *trans*-**156**. The ratio *trans*-**157**:**158** decreased from 10:1 for *trans*-**156** (Table 5, entry 1) to 1:1 for *cis*-**156** (enrty 2).

It is possible to get some broad guidelines from the data in Table 5 on how to predict the relative ratio of dihydrobenzofuran **157** to benzodioxine **158**: $Pd(PPh_3)_2Cl_2$ as a Pd source, lower temperatures (50°C), *trans*-conformation of the phenylpropene double bond favours the formation of rac-*trans*-dihydrobenzofuran **157**, whereas $Pd(OAc)_2$, higher temperatures (80°C) and *cis*-conformation of double bond favours the formation of benzodioxine **158**. The addition of Ph_3P ligand to the reaction catalyzed with $Pd(OAc)_2$ decreased **157**:**158** ratio, but increased combined yield **157** + **158**.

The best yield of compound **157** (42 %, entry 2) and best ratio of **157** : **158** (28 : 1) were obtained under following conditions: 2 eq cinnamic alcohol reacted with 1 eq iodovanilline (excess of cinnamic alcohol (**156**) was used because Ag_2CO_3 readily oxidized one portion of this compound to aldehyde **159**), 6 mol% $Pd(PPh_3)_2Cl_2$, 1,5eq Ag_2CO_3, DMF, 50°C, 3 days.

The addition of H_2O to DMF (ratio 1: 3) and the use of 10 mol% $Pd(OAc)_2$ (entry 6, Table 5) resulted in a decreased yield of **157** (29%) and increased formation of aldehyde **159**.

In order to explain formation of the side products **158**, **159** and **146** a reaction mechanism was proposed (in Scheme 52):

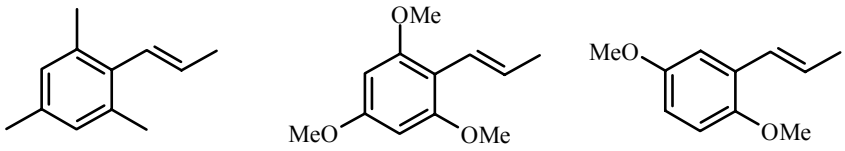


Scheme 52. Proposed mechanism for the palladium catalysed reaction between cinnamic alcohol (**156**) and iodophenol (**119**)

Although the abstraction of the proton from the phenol in the presence of a base should be the fastest reaction (acid-base reaction), it is commonly accepted that this deprotonation step takes place after the oxidative addition of the palladium species to the arylhalide.[84, 86] Moreover, it might also be possible, as depicted in Scheme 52, that deprotonation of a phenol is the initial reaction. After oxidative addition of the palladium catalyst to the aryliodide bond of the phenolate, Ag^+ reacts with the Pd-complex producing insoluble AgI, and a 16-e^- palladium complex. Formation of rac-*trans*-dihydrobenzofuran **157** is depicted in route A, and formation of benzodioxine **158** and cinnamic aldehyde side product (**159**) is presented in route B.(However, an experiment without palladium catalyst showed that Ag_2CO_3 alone is capable of oxidizing cinnamic alcohol (**156**) to aldehyde **159**

under the reaction conditions). Species **I** is responsible for the formation of the thermodynamically more stable *trans*-diastereomer from either *trans*- or *cis*- cinnamic alcohol, because free rotation around the C–C bond in this palladium-intermediate is possible.

Several phenylpropene derivatives presented in Figure 17 have also been examined as the starting material in this reaction. With phenylpropenes having substituents at one or both *ortho*-positions (**160**, **161**) the reaction was inhibited. The increased steric bulk near the double bond is probably responsible for this result because the catalyst and the arylphenol species cannot approach the double bond of alkene properly.

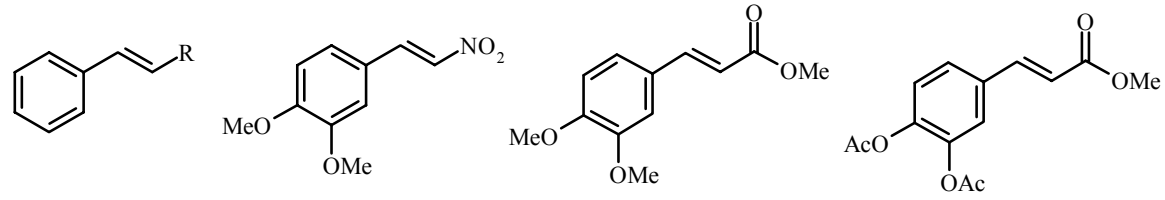


(**160**) (**161**) **(162)**

Figure 17. Phenylpropene derivatives with substituents in positions 2 and/or 6

Electron deficient phenylpropene derivatives (Figure 18) are also not suitable for this reaction: no product was formed when cinnamic acid (**15**), cinnamic aldehyde (**159**) or methyl cinnamate (**163**) were used as starting materials, and they could be reisolated from the reaction mixture. These phenylpropenes with electron pulling groups probably coordinate strongly to palladium, thus inactivating the catalyst as proposed by Fujiwara *et al.*[103]

Several other phenylpropene derivatives (Figure 18) with electron-pulling groups (**164**, **165**, **166**) conjugated with the double bond failed to give any product in the Heck oxyarylation reaction.



(**159**) R= CHO,
(**163**) R = COOMe
(**15**) R = COOH

(**164**) (**165**) (**166**)

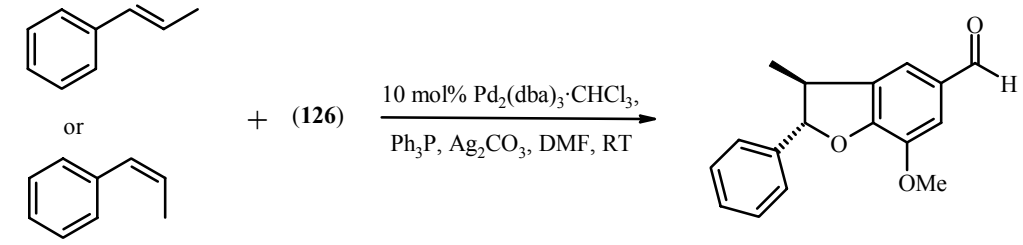
Figure 18. Phenylpropene derivatives not suitable as the substrates for the palladium catalysed Heck oxyarylation reaction

3.1.2.3 The influence of the geometry of the alkene substrate on the stereochemistry of the dihydrobenzofuran product

The question of what influence the geometry of the alkene double bond has on the stereochemistry of the products has already been addressed for the cinnamic alcohol (**156**) as the substrate (Scheme 51, Table 5).

Experiments with *cis*- and *trans*-phenylpropene (**136a**, **b**) have been performed (Scheme 53). In all experiments, with **156** and **136** as starting material, the major product was the *trans*-dihydrobenzofuran (**167**) with the *cis*:*trans* ratio being at least 1:10.

The *trans*-dihydrobenzofuran is the preferred product in the Heck oxyarylation reaction of *cis*- and *trans*-alkenes as starting materials under the reaction conditions. This result is different from the Heck reaction with **136a**, **b** as the starting materials (Scheme 45). As shown in Scheme 45, the geometry of the double bond has an influence on the regioselectivity of the Heck reaction. For the Heck oxyarylation reaction, both isomers of phenylpropene lead to the *trans*-diastereomers of **167**.



trans- (**136a**)
cis- (**136b**)

rac-*trans*-(**167**)
major product

Scheme 53. Heck oxyarylation reaction with *cis*- and *trans*- phenylpropenes

3.1.2.4 Dihydrobezofurans *via* cycloaddition of pseudohalogen phenols

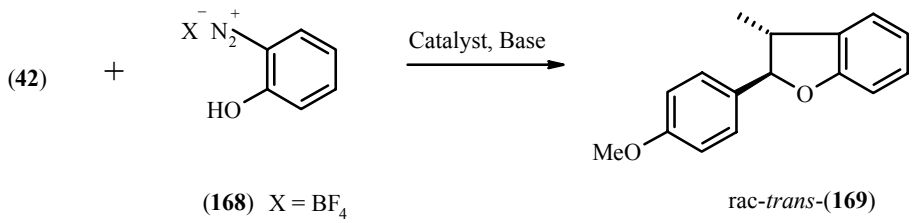
The use of halogenphenols in a palladium catalysed synthesis of dihydrobenzofurans has several disadvantages: first, expensive Ag_2CO_3 must be used as a halogen scavenger in order to generate a cationic palladium intermediate that is thought to be the actual catalyst. Second the presence of silver ion with mild oxidative properties is responsible for the formation of side products such as benzofuran and cinnamic aldehyde (**159**). Furthermore,

the reactions are generally performed at elevated temperature in order to get a satisfactory yield.

Pseudohalides (R-X) such as ArCO-Cl, $ArSO_2$-Cl, $ArN_2^+X^-$, R-OP(O)$(OR_2)_2$, R-OSO_2CF_3 (OTf), R-OSO_2R_f (R_f=perfluoroalkyl), R-OSO_2F, R-OSO_2CH_3 and Ar-ArI^+ undergo an oxidative addition to Pd(0) species. Although all pseudohalides are good leaving groups, they show different reactivities toward Pd(0). Diazonium salts are the most reactive source for the formation of arylpalladium species, the reactions are usually performed at room temperature.[93] Due to their high reactivity these reactions don't need a palladium catalyst stabilised with ligands and are often performed under ligand-free conditions.

The vast majority of the published articles on Heck- and related reactions have been performed on substrates with a terminal double bond.[104] Performing these reactions with substrates having an internal double bond is much less studied because, generally, similar conditions used with the terminal alkenes cannot be applied and because of the regioselectivity problem. A lower yield usually observed for internal alkenes suggests that the arylation is susceptible to steric factor[93] (Scheme 54).

The approach successfully applied with *ortho*-halogenphenols could be also applied for the reactions of pseudohalogen phenols. The model reaction is shown in Scheme 54, with anethole (**42**) and easily accessible *ortho*-phenoxydiazonium tetrafluoroborate (**168**) as the starting materials.



Scheme 54. The model system for the palladium catalysed reactions of diazonium salts and alkenes

Since the aryl-diazonium bond is very susceptible to the oxidative addition in the presence of a palladium catalyst (evolution of N_2 from the intermediate takes place thus generating cationic palladium species in the presence of a non coordinating counter ion) there is no need for halogen scavengers.

In order to determine the best conditions for the catalysed reaction in the model system we chose DMF as a solvent. Thus, as shown in Table 6, temperature, Pd-source, base and ligand have been varied. Initial experiments were performed at 50°C with 4 mol%

$Pd(OAc)_2$ as a catalyst. Several carbonate bases were employed in excess (3 eq) (Table 6, entries 1-4), the product being obtained in low yield only with $CaCO_3$ as a base (3 eq). After establishing the best reaction conditions ($Pd_2(dba)_3{\cdot}CHCl_3$, CH_3CN as solvent, RT), this rather surprising result has been re-examined (entries 5-8) but the calcium carbonate remained the only carbonate base capable of delivering the product.

Table 6. Initial results from the reaction in Scheme 54

Entry	Catalyst	Base (Eq)	Solvent	T[°C]	Yield 169 [GC %]
1	$Pd(OAc)_2$	Na_2CO_3 (3)	DMF	50°	0 %
2	$Pd(OAc)_2$	K_2CO_3 (3)	DMF	50°	0 %
3	$Pd(OAc)_2$	Ag_2CO_3 (3)	DMF	50°	0 %
4	$Pd(OAc)_2$	$CaCO_3$ (3)	DMF	50°	3 %
5	$Pd_2(dba)_3 \cdot CHCl_3$	Na_2CO_3 (3)	CH_3CN	RT	1 %
6	$Pd_2(dba)_3 \cdot CHCl_3$	K_2CO_3 (3)	CH_3CN	RT	3 %
7	$Pd_2(dba)_3 \cdot CHCl_3$	Ag_2CO_3 (3)	CH_3CN	RT	0 %
8	$Pd_2(dba)_3 \cdot CHCl_3$	$CaCO_3$ (3)	CH_3CN	RT	61%

Conditions: 4 mol% catalyst, t = 24 h

After an initial low yield using $CaCO_3$, other parameters were varied. The reaction was performed at 80°C with different palladium sources and ligands (Table 7, entries 1-8), 10% Pd/C and $Pd_2(PPh_3)_2Cl_2$ were equally inadequate for this reaction as $Pd(OAc)_2$, but the breakthrough was the use of $Pd_2(dba)_3{\cdot}CHCl_3$ which gave the product in 25 % yield (entry 2). Several phosphine ligands were tested with $Pd(OAc)_2$ (entries 4-8) among them only $(Cy)_3P$ led to the formation of the product in slightly better yield than the others (10 %, entry 7).

Table 7. Further results from the reaction in Scheme 54

Entry	Load	Catalyst	Base (Eq)	T [°C]	Yield 169 [% GC]	Ligand
1	4 mol%	10% Pd/C	$CaCO_3$ (3)	80°	3 %	–
2	4 mol%	$Pd_2(dba)_3 \cdot CHCl_3$	$CaCO_3$ (3)	80°	25 %	_
3	4 mol%	$Pd(PPh_3)_2Cl_2$	$CaCO_3$ (3)	80°	1 %	_
4	4 mol%	Pd $(OAc)_2$	$CaCO_3$ (3)	80°	3 %	3 eq Ph_3P
5	4 mol%	Pd $(OAc)_2$	$CaCO_3$ (3)	80°	3 %	2 eq Ph_3P
6	4 mol%	Pd $(OAc)_2$	$CaCO_3$ (3)	80°	1 %	3 eq (*o*-Tol)$_3$P
7	4 mol%	Pd $(OAc)_2$	$CaCO_3$ (3)	80°	11 %	3 eq $(Cy)_3P$
8	4 mol%	Pd $(OAc)_2$	$CaCO_3$ (3)	80°	0 %	3 eq Bu_3P
9	10 mol%	Pd $(OAc)_2$	$CaCO_3$ (3)	100°	24 %	_
10	10 mol%	Pd $(OAc)_2$	Ag_2CO_3 (3)	100°	0 %	_
11	10 mol%	Pd $(OAc)_2$	NaOAc (3)	100°	0 %	_
12	10 mol%	Pd $(OAc)_2$	Pyridine (3)	100°	0 %	_
13	10 mol%	Pd $(OAc)_2$	Et_3N (3)	100°	0 %	_
14	10 mol%	Pd $(OAc)_2$	Et_3N (1,2)	100°	0 %	_
15	10 mol%	$Pd_2(dba)_3 \cdot CHCl_3$	$CaCO_3$ (3)	100°	48 %	_
16	10 mol%	$Pd_2(dba)_3 \cdot CHCl_3$	$CaCO_3$ (3)	120°	0 % [a]	_
17	10 mol%	$Pd_2(dba)_3 \cdot CHCl_3$	$CaCO_3$ (3)	120°	0 %	_
18	–	–	$CaCO_3$ (3)	120°	0 %	_
19	10 mol%	Pd $(OAc)_2$	$CaCO_3$ (3)	120°	11 %	_
20	10 mol%	Pd $(OAc)_2$	$CaCO_3$ (5)	120°	8 %	_
21	10 mol%	Pd $(OAc)_2$	$CaCO_3$ (10)	120°	6 %	_
22	10 mol%	$Pd_2(dba)_3 \cdot CHCl_3$	$CaCO_3$ (3)	120°	56 %	_
23	20 mol%	$Pd_2(dba)_3 \cdot CHCl_3$	$CaCO_3$ (3)	120°	48 %	_
24	50 mol%	$Pd_2(dba)_3 \cdot CHCl_3$	$CaCO_3$ (3)	120°	36 %	_
25	10 mol%	$NiCl_2$	$CaCO_3$ (3)	120°	0 %	_
26	10 mol%	$NiCl_2$	$CaCO_3$ (3)	120°	0 %	3 eq Ph_3P

Conditions: 24h, DMF was used as solvent, except in [a] (entry 17) where TBAB was the solvent

An increase of the temperature (100°C) and the amount of the catalyst (10 mol% $Pd(OAc)_2$) led to formation of product in 24 % yield (entry 9). Several non-carbonate bases were tested under these conditions (pyridine, CH_3COONa, Et_3N (3 eq and 1,2 eq), entries 10-14) but not even the traces of the product were formed. Reaction with $Pd_2(dba)_3 \cdot CHCl_3$

under same conditions ($CaCO_3$ used as a base) led, however, to the formation of the product in 48 % yield (entry 15). On the other hand, addition of TBAB to the reaction or using this ionic liquid as the solvent led to complete inhibition of the reaction (entries 16-17).

Variation of the amount of $CaCO_3$ in the reaction with $Pd(OAc)_2$ showed that the yield of the product was slightly lower when more than 3 eq of the base was used (entries 19-21). Since $Pd_2(dba)_3 \cdot CHCl_3$ gave the best results among tested catalysts, the amount of this catalyst was varied at 120°C (entries 22-24). As it can be seen, the higher amount of the catalyst leads to a slightly lower yield, optimum being 10 mol% of the catalyst. $NiCl_2$ as the catalyst, with and without the PPh_3 ligand, did not lead to the formation of the product (entries 25-26).

The trend of obtaining higher yields in palladium catalysed reactions with arenediazonium salts in CH_3CN than in other solvents (NMP, DMF, DMA, EtOH, THF) has been already observed. The explanation for these results was the higher stability of the diazonium salts in acetonitrile than in other examined solvents.[93, 115] Additional experiments performed in acetonitrile (Table 8) showed that the acetonitrile is indeed the solvent of choice for this reaction. This is not only besause of the higher stability of the reaction species along the reaction pathway in acetonitrile on lower temperature (room temperature or 50°C) but the crucial difference lies in the structure of the active palladium species in the solution. Recent work published by Eberlin *et al*. showed that arenediazonium salt and $Pd(dba)_2$ in CH_3CN undergo a time-dependent process involving ligand exchange. As a result of this phenomena, a stable cationic intermediate (Figure 19) having one acetonitrile molecule coordinated as ligand was formed slowly. This intermediate is likely to be the key intermediate in the Heck reaction.[93]

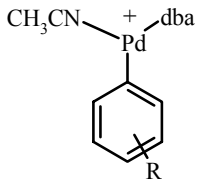


Figure 19. Cationic Pd-intermediate stabilised by coordination of one acetonitrile molecule

Several catalysts have been tested (Table 8 entries 1-5) under the best conditions (3 eq. $CaCO_3$, 20 h) at 50°C. $Pd(OAc)_2$ gave product in 45 % yield, $Pd(PPh_3)_2Cl_2$ (10 mol%, with addition of 10 mol % Zn) in 19 % yield, $Pd_2(dba)_3 \cdot CHCl_3$ in 56 %, $PdCl_2$ in 33 % and $NiCl_2$ (10 mol%) in 7 % yield.

Table 8. Further results from the reaction in Scheme 54

Entry	Load	Catalyst	T [°C]	Yield 169 [% GC]	Remark
1	10 mol%	$Pd(OAc)_2$	50°	45 %	–
2	10 mol%	$Pd(PPh_3)_2Cl_2$ / Zn	50°	19 %	–
3	5 mol%	$Pd_2(dba)_3 \cdot CHCl_3$	50°	56 %	–
4	5 mol%	$PdCl_2$	50°	33 %	–
5	10 mol%	$NiCl_2$	50°	7 %	–
6	10 mol%	$PdCl_2$	50°	49 %	$CaCO_3$ (3 eq)
7	20 mol%	$PdCl_2$	50°	49 %	–
8	50 mol%	$PdCl_2$	50°	43 %	–
9	1 mol%	$PdCl_2$	50°	21 %	–
10	0,1 mol%	$PdCl_2$	50°	7 %	–
11	20 mol%	$NiCl_2$	50°	7 %	–
12	50 mol%	$NiCl_2$	50°	7 %	–
13	–	–	50°	7 %	–
14	–	–	50°	0 %	dioxane
15	–	–	50°	0 %	DMF
16	–	–	120°	0 %	DMF
17	10 mol%	$Pd(OAc)_2$	50°	2 %	dioxane
18	10 mol%	$PdCl_2$	50°	48 %	$CaCO_3$ (1,5 eq)
19	10 mol%	$PdCl_2$	50°	51 %	$CaCO_3$ (5 eq)
20	10 mol%	$Pd_2(dba)_3 \cdot CHCl_3$	RT	25 %	CH_2Cl_2
21	10 mol%	$Pd(acac)_2$	RT	28 %	–
22	5 mol%	$Pd_2(dba)_3 \cdot CHCl_3$	RT	61 %	3 days
23	10 mol%	$Pd(OAc)_2$	RT	32 %	12 h
24	10 mol%	$Pd(acac)_2$	RT	28 %	–
25	10 mol%	$Pd_2(dba)_3 \cdot CHCl_3$	RT	75 %	–
26	10 mol%	$Pd_2(dba)_3 \cdot CHCl_3$	RT	71 %	1,5 eq 42
27	10 mol%	$Pd_2(dba)_3 \cdot CHCl_3$	RT	71 %	$CaCO_3$ (1,5eq)
28	5 mol%	$Pd_2(dba)_3 \cdot CHCl_3$	RT RT	58 %[a] 61 %[b]	16 h 3 days
29	3 mol%	$Pd_2(dba)_3 \cdot CHCl_3$	RT	48 %	–
30	1 mol%	$Pd_2(dba)_3 \cdot CHCl_3$	RT RT	32 %[a] 40 %[b]	3 days 6 days
31	1 mol%	$Pd_2(dba)_3 \cdot CHCl_3$	50°	33 %	10 days
32	1 mol% 2 mol%	$Pd_2(dba)_3 \cdot CHCl_3$ Ph_3P	RT RT	21 %[a] 30 %[b]	20 h 3 days
33	0,1 mol%	$Pd_2(dba)_3 \cdot CHCl_3$	RT	10 %	3 days
34	5 mol%	$Pd_2(dba)_3 \cdot CHCl_3$	0°	55 %	16 h
35	10 mol%	$PdCl_2$	50°	6 %	(+)-α-Pinene
36	10 mol%	$PdCl_2$	50°	6 %	(–)-α-Pinene
37	10 mol%	$Pd(BINAP)Cl_2$	RT	4 %	(+)-(R)-BINAP
38	10 mol%	$Pd_2(dba)_3 \cdot CHCl_3$	RT	60 %	Compound **170**

Conditions: 1,2 eq anethole, reaction time 20 h, 3 eq $CaCO_3$ (if not otherwise stated), for solvents different than CH_3CN see remark, for ligands see remark, for different conditions see remark; [a] the samples were taken and the reaction continued, [b] samples taken from the same reaction as [a]

Experiments with $PdCl_2$ and $NiCl_2$ have been performed with the catalyst amount increased to 50 mol% (entries 6-7-8, 5-11-12) with the conclusion that the optimal amount of the catalyst is 10 mol%. Decrease of the $PdCl_2$ amount to 1 mol% and 0,1 mol% led to decrease in the yield (entries 9, 10), but still producing the desired product in satisfactory 21 % yield (experiment with 1 mol% catalyst). In the case of $NiCl_2$, the amount of the product formed (7 %) remained the same with different catalyst loads so the blind reaction (without catalyst) was performed with the surprising result that the product was formed in 7 % yield (entry 13). Other blind tests (entries 14-16) showed that without catalyst no product was formed in any other solvent. This result points out that CH_3CN is not only involved in the active catalytic species but also enables formation of the product even in the absence of the catalyst.

The influence of the solvent seems to be more important than the temperature: reaction performed in dioxane (entry 17) yielded only 2 % of the product, whereas the reaction performed in CH_3CN under identical conditions yielded **169** in 45 % yield (entry 1).

Since the higher temperature can lead to decomposition of the diazonium salt, reactions were performed at room temperature with 10 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ in dichloromethane and acetonitrile (entries 20 and 25) yielding 25 % and 75 % product respectively. One reaction was also performed at 0°C with 5 mol% catalyst yielding 55 % product after 16 h (entry 34).

The amount of the base was varied in order to find the optimal amount (entries 6, 18, 19, 25, 27). The conclusion is that the increase to 5 equivalents or the decrease to 1,5 equivalents of base both lead to a slightly decreased yield with different catalysts at 50°C as well as at room temperature.

An increase of the amount of anethole from 1,2 to 1,5 equivalents led to a slightly reduced yield (entries 25, 26), probabe reason being coordination of the alkene to the catalyst.

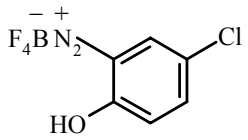
With a lower load of the catalyst, the reaction time was prolonged from 20 h to several days (entries 28, 30, 31, 32, 33). The majority of the product was, however, formed within the first 20 hours of the reaction.

A decrease of the catalyst load ($Pd_2(dba)_3{\cdot}CHCl_3$) led to decreased yield: 5 mol% catalyst gave 58 % yield (entry 28), 3 mol% catalyst gave 48 % yield (entry 29), 1 mol% catalyst gave 32 % yield after 3 days (entry 30), 0,1 mol% catalyst gave 10 % yield after 3 days (entry 33). Addition of 2 mol% Ph_3P to the reaction of 1 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ led to a slightly decreased yield of 30 % after 3 days (entry 32).

The addition of chiral α-pinene ligands to the reaction catalysed with $PdCl_2$ (entries 35-36) led to significantly lower yields than reaction in the absence of ligand (entry 6), a low yield (4,5 %) was also observed with $Pd(BINAP)Cl_2$ as the ligand (entry 37), in the range of the blind reaction.

The best yield (75 %, entry 25) was obtained with 10 mol% $Pd_2(dba)_3 \cdot CHCl_3$ catalyst, 1,2 eq anethole, 3 eq $CaCO_3$ base in acetonitrile at room temperature after 20 hours. The variations on the amount of the reactants, temperature or solvent led to a reduced yield.

The diazonium compound **170** having one chlorine atom attached to the aromatic moiety was also tested, under the best reaction conditions a new peak in GC was observed, and the product yield was 60 % (entry 38: 10 mol% $Pd_2(dba)_3 \cdot CHCl_3$, 3 eq $CaCO_3$, CH_3CN, RT, 20h).



(**170**)

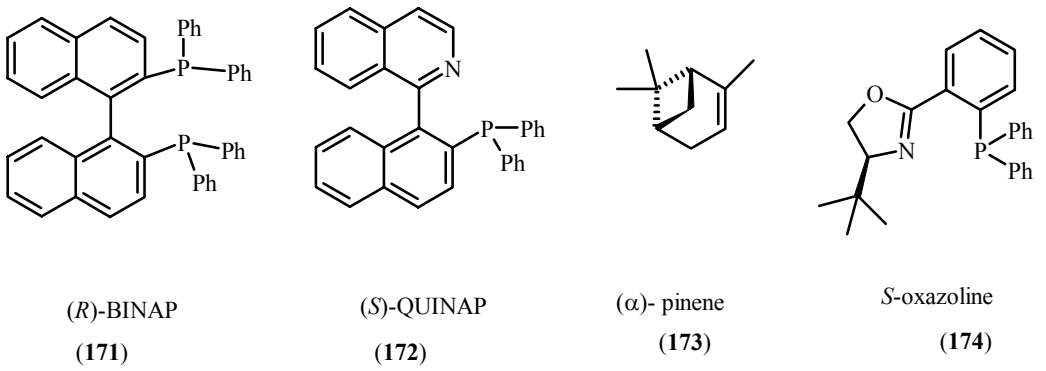
Figure 20. Diazonium compound **170** having one chlorine atom

The conditions for the Heck oxyarylation reaction were successfully optimised for the synthesis of dihydrobenzofuran compounds in one step in up to 75 % yield. The choice of solvent and base plays crucial role in this reaction, catalyst and temperature are also very important for high yields. Addition of phosphine ligands slows the reaction resulting in lower yields or even total inhibition. A suggested structure of active catalytic species (Figure 19) offers an explanation for low yields with chiral diphosphine ligand (*R*)-BINAP and α-pinene ligands. In the presence of these ligands, this active catalytic species cannot be formed (since the ligands occupy coordination sites on palladium), the reaction takes another course (involving different palladium species), resulting in lower yield.

Easily accessible diazonium salts as starting material have advantages over *ortho*-halogenphenol derivatives investigated previously: a higher yield wes obtained and reactions were performed at room temperature.

3.1.2.5 Palladium catalysed cycloaddition reaction in the presence of chiral ligands

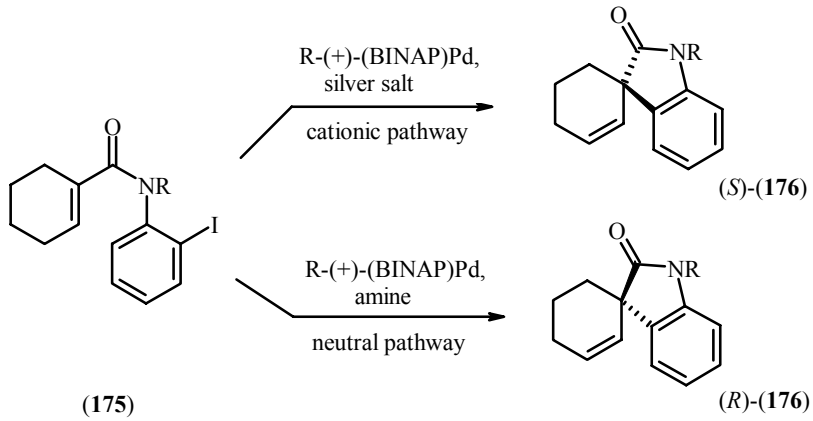
The approach to *trans*-dihydrobenzofurans *via* a palladium catalysed Heck oxyarylation offers the possibility to employ chiral ligands in order to control the absolute configuration of the product. Complexes with chiral ligands have been prepared from $Pd_2(dba)_3 \cdot CHCl_3$ or $Pd(COD)Cl_2$; some often used chiral ligands in palladium catalysed reactions are (Figure 21):



(*R*)-BINAP (**171**) (*S*)-QUINAP (**172**) (α)- pinene (**173**) *S*-oxazoline (**174**)

Figure 21. Some often used chiral ligands for palladium catalysed reactions

Overman *et al*.[106] made observations by showing that from (E)-α,β–unsaturated 2-iodoanilides (**175**) either enantiomer of the Heck product could be formed using a single enantiomer of a chiral diphosphine (*R*)-BINAP Scheme 55:

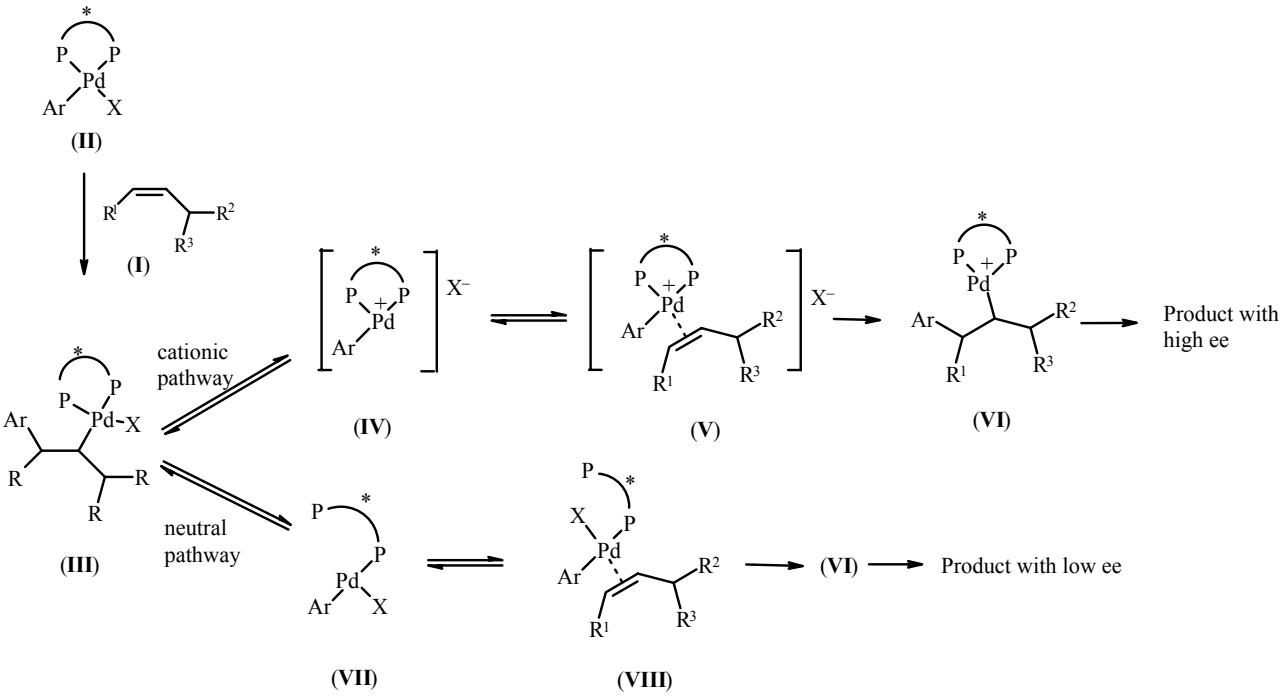


(**175**)

Scheme 55. Both enantiomers of **176** formed from R-(+)-BINAP under different reaction conditions

Cyclisation in the presence of a halide scavenger such as a silver salt makes the reaction proceed *via* cationic pathway, whereas cyclisation in the presence of a tertiary amine as a base gives rise to the neutral pathway. This example shows how minor changes in the reaction conditions can lead to different reaction mechanisms and to different products. In some cases, the use of Ag_3PO_4 had some advantages over Ag_2CO_3, better yields and higher ee were obtained.[107]

The asymmetric intramolecular Heck reaction became a standard tool in the natural product total synthesis[108]. The key step in the catalytic cycle of the asymmetric Heck reaction[109] (AHR) with regard to enantioselectivity is coordination followed by *syn*-insertion of the alkene substrate (**I**) into the Pd-Ar bond of **II** to give **III** (Scheme 56):

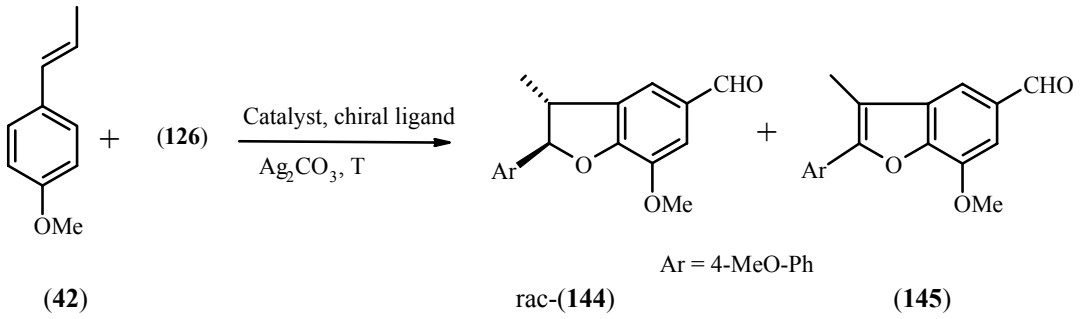


Scheme 56. Cationic and neutral pathways for the asymmetric Heck reaction

The species **III** can participate in two different reaction pathways, depending on the reaction conditions. The cationic pathway begins with the dissociation of X^- from **III** to generate tri-coordinate 14-e^- cationic complex **IV** with X^- as the counterion. Complexation of the alkene compound (**I**) into the vacant site (on Pd) gives the 16- e^- species **V**. Insertion of the alkene compound (**I**) into the Pd–Ar bond is followed by reformation of the Pd–X bond, giving **VI** which would be transformed to the final product. The chiral bidentate ligand remained fully chelated (attached to Pd with both phosphorous atoms) throughout this

reaction pathway providing a maximum asymmetric induction. The alternative, neutral pathway commenced with the dissociation of one arm of the bidentate ligand giving the neutral species **VII**. Association and complexation of the alkene into the vacant site of the metal catalyst gives the neutral species **VIII**, which after alkene insertion into the Pd–Ar bond and re-complexation of the previously displaced phosphine moiety also gives **VI**. The partial dissociation of the chiral ligand during the neutral pathway makes this route less suited for a high asymmetric induction. Most asymmetric Heck reactions reported so far indicate that conditions that favour the cationic route also give better enantiomeric excess of the product. The nature of X in ArX (and thus the strength of Pd–X bond in **III**) is a very important factor, for X = halide both routes are possible depending on reaction conditions, for X = triflates or diazonium salts the cationic pathway is favoured. It is possible to influence which pathway will be followed in a given Heck reaction either by adding a "halide scavanger" to the reaction of aryl halides (usually silver(I) salt that leads to formation of low soluble AgX replacing the halide with its own anionic component), or by adding excesses of halide anions to reactions where triflates were used (resulting in nucleophilic displacement of the triflate anion from **III)**.

The reaction of *ortho*-halogenophenols with anethole has been examined first (Scheme 57). The chiral bidentate phosphine ligand (*R*)-BINAP (**171**) was active at 80°C (Table 9, entry 1), but there was no reaction at 50°C or room temperature. After 24 h at 80°C with (*R*)-BINAP as the chiral ligand, 7-methoxy-2-(4-methoxy-phenyl)-3-methyl-2,3-dihydro-benzofuran-5-carbaldehyde (**144**) was formed in 29 % yield and 7-methoxy-2-(4-methoxy-phenyl)-3-methyl-benzofuran-5-carbaldehyde (**145**) in 17 % yield. HPLC analysis with chiral column (chiracel OD-H) showed that only racemic compound has been formed.



Scheme 57. Reaction of anethole (**42**) and iodovanilline (**126**) catalysed with chiral ligands

Table 9. Results from the reaction on Scheme 57

Entry	Catalyst	Ligand	Solvent	T [°C]	Yield 144/145 [% GC]
1	$Pd_2(dba)_3 \cdot CHCl_3$	(*R*)-BINAP	DMF	80°	29 / 17
2	$Pd_2(dba)_3 \cdot CHCl_3$	(*S*)-Quinap	DMF	50°	13 / 24
3	$Pd_2(dba)_3 \cdot CHCl_3$	(*S*)-Quinap	DMF	80°	31 / 24
4	$Pd(Ph_3P)_4$	(*S*)-Quinap	DMF	80°	0 / 0
5	$Pd(OAc)_2$	(α)-Pinene	toluene	50°	21 / 11
6	$Pd_2(dba)_3 \cdot CHCl_3$	Oxazoline	DMF	50°	0 / 0

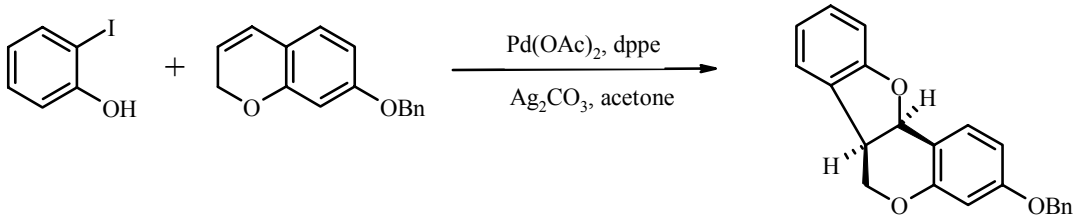
The reaction performed with (*S*)-Quinap (**172**) at 50°C yielded 24 % of benzofuran **145** and 13 % of *trans*-dihydrobenzofuran **144** (entry 2). Benzofuran was the major product with this ligand at 50°C whereas at 80°C the ratio swiched to 31 % **144** / 24 % **145** (Entry 3)

Two experiments were performed in order to test the influence of the palladium source in this reaction using $Pd_2(dba)_3 \cdot CHCl_3$ and $Pd(Ph_3P)_4$ as catalysts and (*S*)-Quinap ligand (**171**) (entries 3 and 4). With $Pd(Ph_3P)_4$ there was no product formation even at 80°, whereas under the identical conditions $Pd_2(dba)_3 \cdot CHCl_3$ yielded 31 % of racemic *trans*-dihydrobenzofuran **144** and 24 % benzofuran **145**. Strongly coordinating phosphine ligands are probably occupying all coordination sites on the $Pd(Ph_3P)_4$ catalyst making this the reason for inhibition of the reaction. Pinene ligand (**173**) also facilitated the cycloaddition reaction in toluene as the solvent at 50° forming 21 % of racemic *trans*-dihydrobenzofuran **144** and 11 % benzofuran **145** (entry 5). Oxazoline ligand **174** was unable to induce the formation of the product; the nitrogen atom may be responsible for this result since amine bases (Et_3N and pyridine) inhibited formation of the product in earlier experiments.

In the reaction with iodovanilline (**126**), the best yield of dihydrobenzofuran **144** was obtained with (*S*)-Quinap (**172**) (entry 3) but the product was a racemic mixture. The obtained yield with this bidentate ligand was significantly lower than the yields with Ph_3P or in the phosphine-free reaction under same reaction conditions.

This rather surprising result was confirmed independently in a study published by Antus *et al.* [110] during our research. The authors studied the Heck oxyarylation reaction used to synthesise 3-benzyloxypterocarpan (**149**) in the presence of chiral phosphine ligands, a chiral ionic liquid and (+)-α-pinene as chiral ligand. The Heck oxyarylation reaction of 7-benzyloxy-2H-chromene (**120**) and 2-iodophenol (**119**) has been already performed[111] with

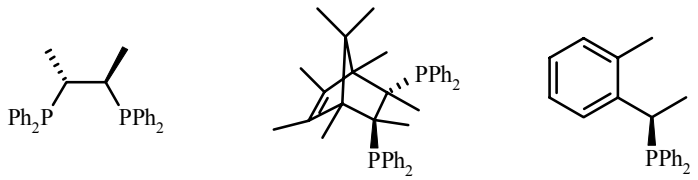
1,2-bis(diphenylphosphino)ethane (dppe) as the ligand and Ag_2CO_3 as a base, providing pterocarpan (**121**) in 49 % yield (Scheme 58).



(**119**) (**120**) 49% rac-*cis*-(**121**)

Scheme 58. Heck oxyarylation reaction yielding pterocarpan **121**

It could be expected that change of the achiral diphosphine ligand with optically active phosphine ligands would result in an optically active product (**121**). Three chiral bidentate phosphine ligands; 2*R*,3*R*(+)-bis(diphenylphosphino)butane (CHIRAPHOS) (**177**), *trans*-2*S*,3*S*-bis(diphenylphosphino) bicyclo[2.2.1]-hept-5-ene (NORPHOS) (**178**), (*R*)-BINAP (**171**) and a monodentate phosphine ligand, *R*-1-[2´-diphenylphosphino]phenyl-methoxyethane (TRIPHOS) (**179**) (Figure 22) were tested in this reaction.



(2R,3R)-(+)-(**177**) CHIRAPHOS (2S,3S)-(+)-(**178**) NORPHOS (R)-(+)-(**179**) TRIPHOS

Figure 22. Chiral ligands employed in Heck oxyarylation reaction to pterocarpans

Surprisingly, and in contrast to the acceptable 49 % yield with achiral dppe as the ligand, the reaction with chiral phosphine ligands gave very low yields and very small ee (5-10 %).

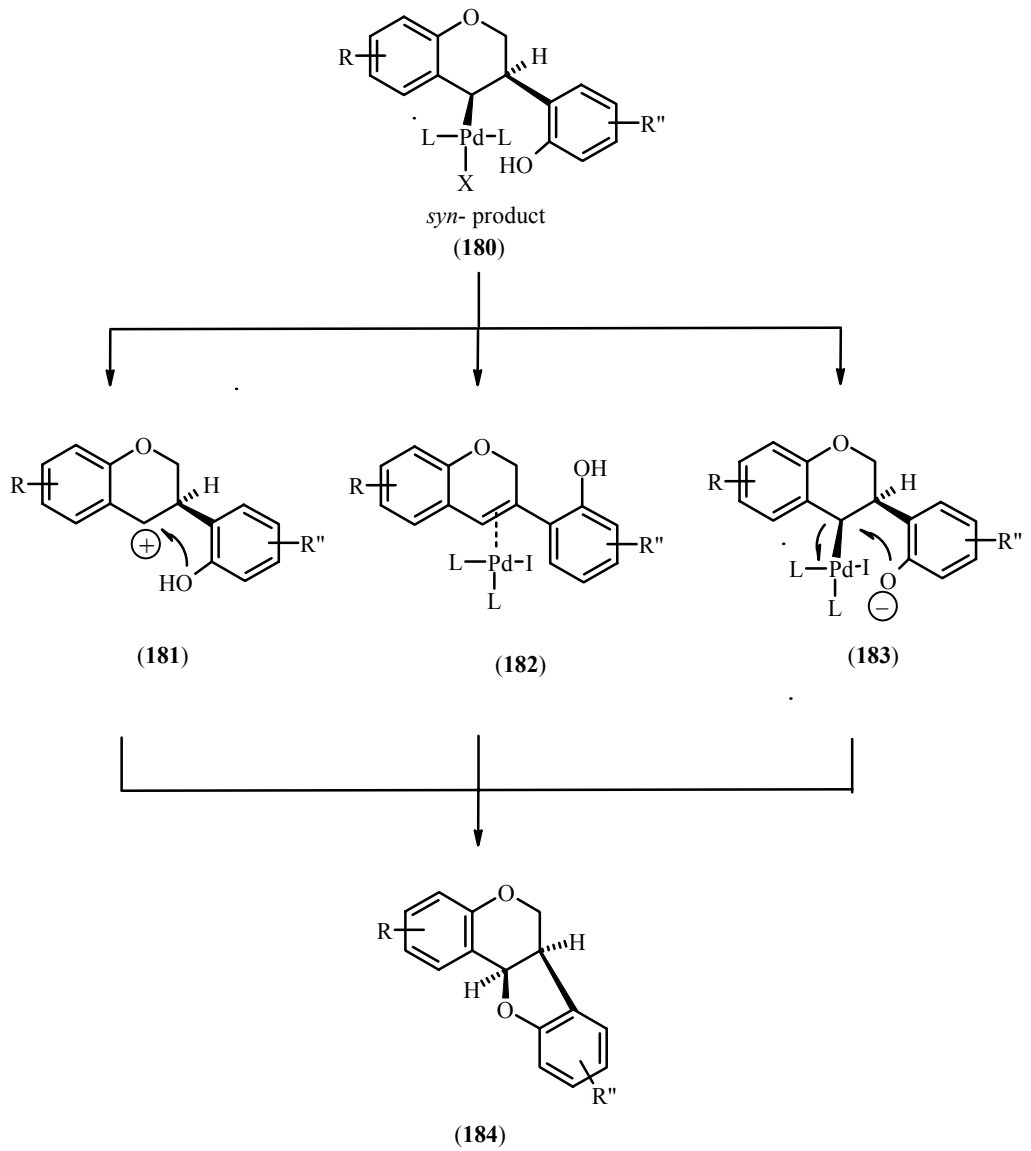
It was found that the CHIRAPHOS, NORPHOS and TRIPHOS slightly preferred the formation of the *S*,*S* isomer and (*R*)-BINAP preferred the *R*,*R* isomer. Active palladium species were generated *in situ* with chiral ligands. It was also surprising that the

commercially available chiral palladium complex Pd[(*R*)-BINAP]Cl_2 showed no selectivity and led to racemic product **121**.

Ionic liquids, besides being a suitable solvent for Heck reactions, could form a carbene-palladium complex[112] which was found to be the actual catalyst, thus enabling Heck reaction without phosphine ligands and giving the product **121** in 13 % yield with 5 % ee. The addition of Ph_3P (entry 7) resulted in significantly increased yield (45 %) but the chiral induction was completely lost. This result indicates that the chiral ionic liquid was completely exchanged by achiral Ph_3P in the palladium catalytic species.

Since it was previously reported[113] that a complex consisting of palladium acetate and(+)-α-pinene was able to catalyse the intramolecular ring closing reaction of phenol derivative, the authors have tested the (+)-α-pinene chiral ligand with both acetone and an achiral ionic liquid [bmim][PF_6] as the solvent in the Heck oxyarylation reaction. Although the reactions with (+)-α-pinene led to a racemic mixture, the reaction in an ionic liquid provided the highest yield (71 %) of the racemic product obtained for the Heck oxyarylation reactions to pterocarpans.

The reaction mechanism for this reaction is not fully understood, it was proposed that the reaction proceeds *via* oxidative addition of aryl iodide to Pd(0), followed by regioselective *syn*-addition and palladium displacement by the phenolic oxygen whose details are not known (Scheme 59). On the basis of the data published in the literature,[110] the displacement step may take place *via* (i) cationic (**181**), (ii) neutral (**182**) or a palladium containing cyclic intermediate (**183**) as shown in Scheme 71. In order to investigate step **180→184** the chiral ligands were used. Thus, if this step proceeds *via* pathway (i) (**180→181→184**) or pathway (iii) (**180→183→184**) an asymmetric Heck oxyarylation of pterocarpans **184** would be achieved. Since there was very small (or even a lack of) selectivity observed during asymmetric oxyarylations to levo- or dextrorotatory pterocarpans (6a*R*, 11a*R*)- **184** or (6a*S*, 11a*S*)- **184** the pathways (**180→181→184**) and (**180→183→184**) could be ruled out as the main pathways. Therefore, the σ-benzylpalladium intermediate **180** is probably first transformed to the carbocation **182** and then the chirality induced by the *syn*-addition step (addition of the palladium species on the alkene forming **180**) is lost during its transformation to the π-benzylpalladium complex **182** by the removal of the 3-H that results in rac-pterocarpan **184**.

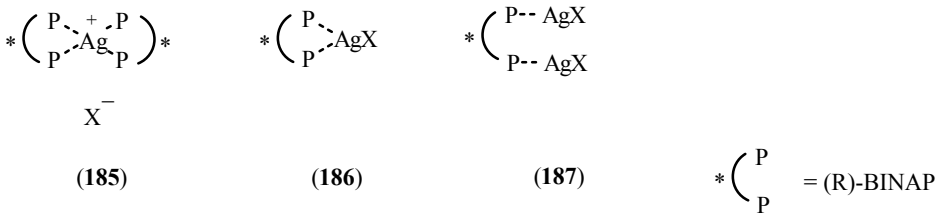


Scheme 59. Possible pathways of the displacement step

The results published by Antus *et al.*[110] support the hypothesis that the formation of pterocarpan **184** takes place through an achiral intermediate, possibly the intermediate **182**, thus explaining the unexpectedly small selectivities with chiral ligands.

Other possible reasons that the reaction with chiral diphosphine ligands such as (*R*)-BINAP leads to racemic product could be the presence of excess Ag^+ cations in the reaction mixture. Since silver carbonate is the base and palladium is the catalyst, the actual ratio of (Ag^+) : (Pd) is 3 eq : 0,1 eq = 30 : 1. Yamamoto and Momiyama[114] published that they were able to isolate three different silver-(*R*)-BINAP complexes in THF (**185**, **186**, **187**, Scheme 60). These complexes were examined as the catalyst in the nitroso aldol synthesis of tin enolates. Either the complex **185** or **187** could be selectively generated from 2

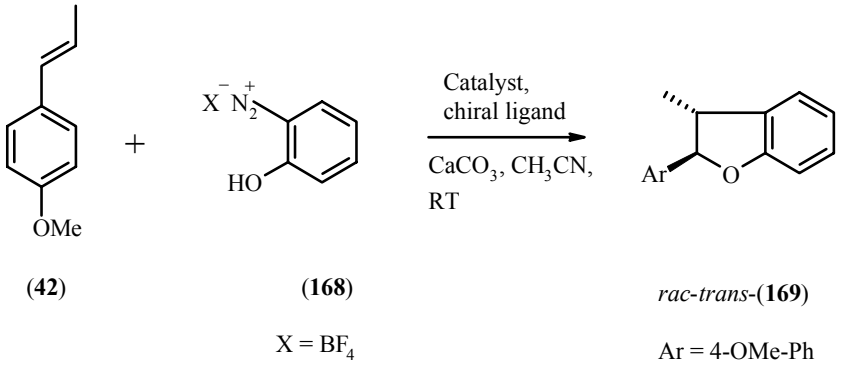
equivalents of (*R*)-BINAP or 0,4 equivalents of (*R*)-BINAP for AgOTf, respectively. The generation of the 1:1 complex was highly dependent on the choice of silver anion, and was obtained almost exclusively by switching the silver salt from AgOTf or $AgClO_4$ to AgOAc or $AgOCOCF_3$.



Scheme 60. Different silver-(R)-BINAP complexes

Since the reaction conditions for palladium catalysed Heck oxyarylation reaction require high Ag^+ content, it seems reasonable to conclude that Ag^+ (which is isoelectronic with palladium atom) could be responsible for formation of the racemic product by interacting with the chiral ligand along the reaction pathway.

The reaction of diazonium salt **168** and anethole (**42**) (Scheme 54) was repeated in the presence of the chiral ligands (Scheme 61). This reaction gave very low yields of **169** under these conditions as presented in Table 12.



Scheme 61. Reaction performed in the presence of chiral ligands

Addition of the chiral (α)-pinene ligand (**173**) to the reaction catalysed with $PdCl_2$ (Table 10, entries 1-2) led to a significantly lower yield (6 %, entries 1, 2) than the reaction without ligand (49 %, Table 2, entry 6). A low yield of only 4 % was also observed with $Pd(BINAP)Cl_2$ as the catalyst (entry 3). In all cases these chiral ligands led to the formation of racemic product **169**.

Table 10. Reaction of anethole with diazonium compound (**168**) in the presence of chiral ligands

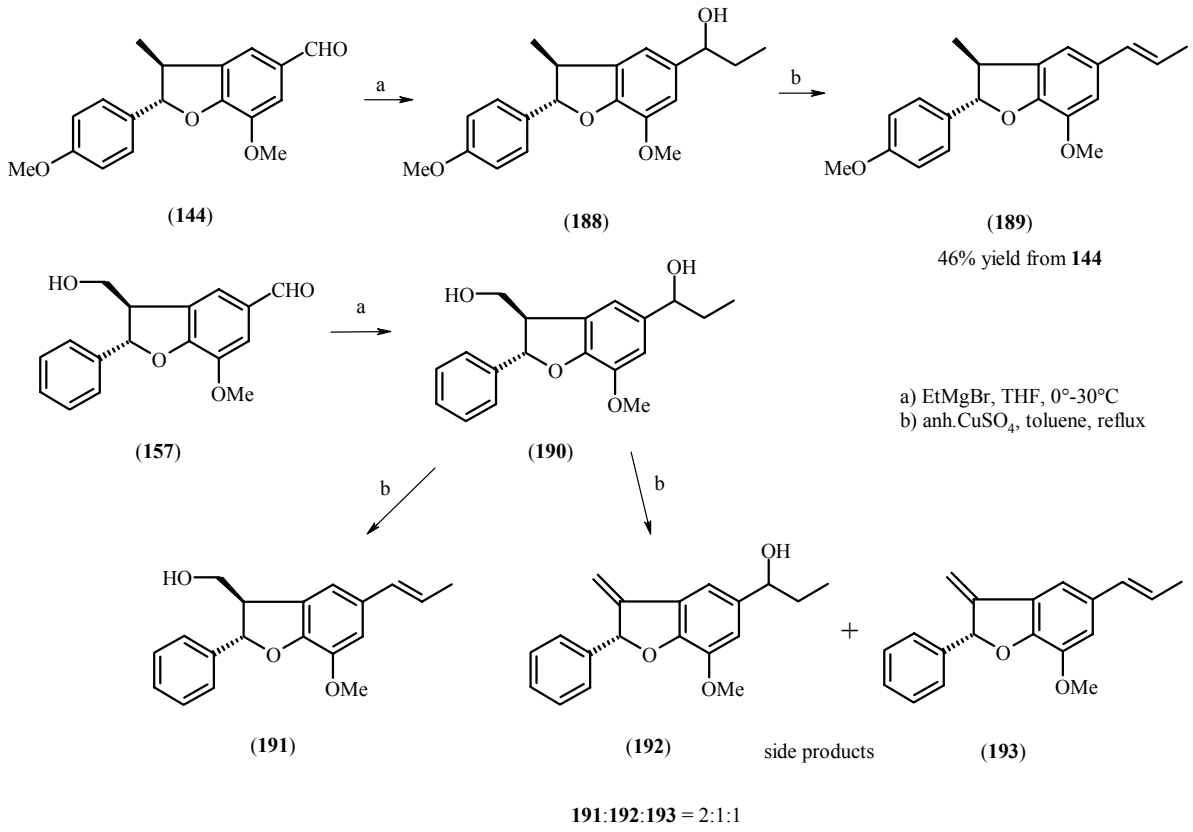
Entry	Load	Catalyst	Ligand	Base [Eq]	Solvent	T [°C]	Yield 169 [% GC]
1	10 mol%	$PdCl_2$	(+)-α-pinene	$CaCO_3$ (3)	CH_3CN	50°	6 %
2	10 mol%	$PdCl_2$	(–)-α-pinene	$CaCO_3$ (3)	CH_3CN	50°	6 %
3	10 mol%	$Pd(BINAP)Cl_2$	–	$CaCO_3$ (3)	CH_3CN	RT	4 %

The probable cause for the lack of stereoselectivity is the mechanistical pathway involving an achiral intermediate, similar to Heck oxyarylation reaction to pterocarpans.

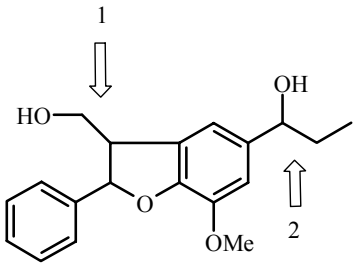
3.1.2.6 Transformation of aldehyde side chain of dihydrobenzofuran compounds - Approach to neolignan derivatives

The palladium catalysed cycloaddition reaction described in the former chapters is a straightforward approach to compounds with a dihydrobenzofuran skeleton. Some natural neolignans from the perseal class have this basic structure of a dihydrobenzofuran moiety with an aldehyde group at C(1') of the aromatic ring. The –CHO group offers the possibility to easily convert this functional group to other functionalities; the Grignard reaction with EtMgBr was performed on **144** and **157**. Another often used approach to derivatives with side chain other than an aldehyde group would be the Wittig reaction.[32] With this reaction, however, the *trans*/*cis*-ratio of the formed double bond is sometimes problematic. As can be seen in Scheme 62 the addition reaction of ethyl Grignard-reagent to aldehyde group led to formation of **188** and **190**, respectively. Two equivalents of Grignard reagent were used with **157** because the first equivalent reacted with the –OH group of this compound. The next step was the $CuSO_4$ catalysed water elimination with formation of the double bond conjugated with the aromatic ring (**189** and **191**). The compound **189** was obtained after purification in 70 % yield from **188.**

The water elimination reaction of **190** resulted in the formation of a mixture of products **191**, **192** and **193**, which were formed because of two possible reaction sites (Scheme 63) under the applied conditions; the compound **188,** formed from anethole, showed no problem with this reaction because of the lack of a hydroxyl group.



Scheme 62. Transformation of aldehyde group to propene side chain



Scheme 63. Two possible reaction sites for compound **191**

CHAPTER 4 CONCLUSIONS

The experiments performed during this study show that the Heck oxyarylation reaction can be successfully applied for the palladium-catalysed preparation of compounds having a dihydrobenzofuran moiety. The aldehyde group on the halogen vanilline is not only tolerated, but also activate in this reaction and allows easy conversion to other functional groups in the obtained dihydrobenzofuran compound. Several examined phenylpropenes are also suitable for this reaction, allowing the Heck oxyarylation reaction to become a synthetic approach to compounds having a dihydrobenzofuran moiety.

This synthetic approach to neolignans allows construction of different derivatives by choosing the phenylpropene unit for the cycloaddition reaction and by choosing the modification of the side chain.

In order to obtain good yields, some guidelines are useful:

1) The nature of the alkene plays a very important role; compounds having a double bond conjugated with electron-pulling groups are not suitable for this reaction, no product was formed. Cinnamic alcohol (**156**) is a suitable substrate but some side products like cinnamic aldehyde (**159**) and benzodioxine (**158**) are formed in the course of the reaction. In order to avoid formation of these side products, anethole (**42**) was used as the substrate. In this case, however, a benzofurane side product (**145**) has been isolated.

2) Iodovanilline was successfully applied in this reaction. Bromovanilline was also able to form products at temperatures over 80°C, but with strong preference for the formation of benzofurans as the major product.

3) The choice of the base is crucial for successful cyclisation: Ag_2CO_3 is the base of choice for the reaction with halogenophenols, $CaCO_3$ is the base of choice for the reaction with diazonium salts.

4) Aryl diazonium salts are more reactive than arylhalides and the reaction can be performed at room temperature. With these substrates, Ag^+ bases become obsolete and a benzofuran side product was not formed. However, reaction conditions are very important: $CaCO_3$ is the only base able to afford dihydrobenzofurans in reasonable yields, CH_3CN is the solvent of choice.

The reactions of diazonium salts as the starting materials in the presence of chiral ligands have been also examined. The racemic products were obtained in lower yields

compared with the ligand-free reactions. A probable reason for this lack of selectivity is the formation of the achiral intermediate along the reaction pathway.

In the reactions of iodovanilline and anethole in the presence of chiral ligands, the products were obtained in a lower yield and as a racemic mixture. This result, lower yields and lack of selectivity, is consistant with the published results for the similar reaction (Scheme 59). It was proposed that an achiral intermediate is responsible for the lack of selectivity; applied chiral ligands coordinate strongly to the catalyst, thus diminishing the yield of the product.

OUTLOOK

After the general reaction conditions have been established, variations in the side chain and in the substitution pattern of the phenylpropenes should allow access to many natural products and new derivatives having a dihydrobenzofuran moiety.

Screening the ligands in this reaction should point out the ones that lead to acceleration of the reaction (in this study, the ligand-free reactions gave higher yields of the products, because the catalytic species had enough empty coordination places to catalyse the reaction. Ligands that have been examined were probably coordinated to the catalytic species too strong, leaving not enough unoccupied coordination places on the catalytic species to allow the oxyarylation reaction to take place). Furthermore, screening of the chiral ligands under the appropriate conditions should result in the identification of the ones that could stereoselectively form the dihydrobenzofuran compounds.

The role of the base in the mechanism is not clarified, further experiments should give the answer to the questions of why Ag_2CO_3 (in the reactions with halogenphenols) and $CaCO_3$ (in the reactions with diazonium compounds) are the only bases suitable for the oxyarylation reaction with phenylpropenes.

Initial experiments performed with diazonium salts having different anions (BF_4^-, PF_6^-) show that the anionic component of the diazonium salt could influence the reaction yield,[115] further studies are needed.

CHAPTER 5 EXPERIMENTAL PART

5.1 GENERAL INFORMATIONS

Melting points were measured on Electrothermal 9100 and are uncorrected. IR spectra were recorded on FT-IR 16 PC Perkin-Elmer. Spectra from liquid substances were recorded as film between NaCl plates; solids were recorded in a form of KBr pill. UV spectra were recorded with a Shimadzu UV-160A, solutions with concentrations C=0,1 mg/ml in appropriate solvent were used. NMR spectra were recorded at 300 MHz on a Bruker Avance 300 Spectrometer using TMS as the internal standard and $CDCl_3$ as a solvent. Chemical shifts (δ) are presented in ppm. Coupling constants are given in Hz. Multiplicities of signals are abbreviated in the following way: s – singlet, d – doublet, t – triplet, m – multiplet, ws – wide singlet, dd – doublet of doublets, etc. Mass spectra were recorded on mass-spectrometer Finnigan SSQ 710 (EI – ionisation). Gas chromatography was performed on Shimadzu GC-14A, using a HP-5 column (J & W Scientific) with a FID detector. Thin layer chromatography (TLC) has been performed on commercial Silica gel plates from Merck (Silica gel 60 F_{254}) that are UV-active (254 nm). TLC plates were afterwards dipped in a solution of Molybdatophosphorous acid and Ce(IV)sulphate in 4% sulphuric acid. Upon heating, organic substances were oxidised giving blue spots on a white to light blue background. The chiral HPLC column Chiracel OD-H (Daicel) was used.

Column-chromatography separations were performed using Silica gel 60 (0,040-0,064 mm particle size) from Merck. Mixtures of hexane / ethyl acetate and toluene / ethyl acetate were used as eluents.

The solvents were distilled prior to use; dry solvents were prepared according to published procedures.[116] If not stated otherwise, reactions were performed in dry solvents under argon atmosphere and organic phases (layers) were dried over $MgSO_4$. All substances that are not described in the following synthetic procedures have been obtained from commercial suppliers (Acros, Aldrich, BASF, Fluka, Lancaster, Merck-Schuchard, Riedel de Haen or Roth).

Preparation of the samples for GC**:** Samples (0,2 ml) were taken with a syringe and added to 2 ml of unsaturated $NaHCO_3$ solution. Organic compounds were extracted with 2 ml ethyl acetate, dried over $MgSO_4$, filtered and filled in the GC vials.

4.2 PREPARATION PROCEDURES:

Typical procedure for preparation of (tetraisopropyl)phosphorodiamidous acid-(2-ethyl) phenyl ester (**86c**) :

Bis(*N*,*N*-diisopropylamino)chlorophosphine (**93**) (1,33g, 5 mmol) was placed in a dried flask under nitrogen. 10ml of dry THF was added, followed by Et_3N (2,08 g, 2,0 mmol). Solution of 2-ethylphenol (**105**) (2,4 g, 2,05 mmol) in dry THF was added dropwise through the syringe to the reaction mixture. After 6 hours of reflux, TLC showed no remaining starting material. Solid NH_4Cl was added to the mixture to quench the reaction. After filtration and evaporation of the solvent, 1,78 g of yellow oil was obtained. Purification on the silica gel column using petrolether:ethylacetat = 4:1 as the eluent resulted with decomposition and incomplete separation of the products. However, the following compounds (**97**, **108**) have been identified by their signals in NMR and mass spectrometry:
NMR ^{1}H: (δ) t 1,19 3H (C**H**$_3$-CH$_2$-), dd 1,33 12H (**H**$_3$C-CH-C**H**$_3$), q 2,68 2H (CH$_3$-C**H**$_2$-), m 3,6 1H (H$_3$C-C**H**-CH$_3$), s 6,0 1H (**H**O-), m 7,05-7,35 4H (Ar**H**);

Preparation of bis(*N*,*N*-diisopropylamino)chlorophosphine (**93**):

Diisopropylamin (**98b**) (29,5 g, 0,29 mol) in 80 ml of Et_2O was cooled to 0°C and PCl_3 (10,0 g, 72 mmol) was added dropwise under strong stirring. Reaction was conducted under N_2 atmosphere. After 2 hours reflux, the mixture was stirred for an additional 2 hours at room temperature. White suspension was filtered and precipitate was washed several times with ether. Organic solvent was evaporated on rotary evaporator under reduced pressure. Yellowish crystals were obtained as the raw product (13,0 g, 67 % yield). The obtained raw product could be purified by sublimation at 90°C, p=1 mbar yielding white crystals of bis(N,N-diisopropylamino)chlorophosphine (**93**) (4,5 g of the raw product was purified in the described way and 430 mg of pure white crystals were obtained after the first try. In the second try 480 mg were obtained. Since the purified substance crystalised on the cooling finger of the cooler, the yield was very dependent on the handling - the obtained crystals were shock sensitive and could easily fall "back" to raw product).
NMR ^{1}H: (δ) d 1,47-1,50 24H (**H**$_3$C-CH-C**H**$_3$), m 3,35-3,44 4H (H$_3$C-C**H**-CH$_3$); ^{13}C: (δ) 19,22 (**C**H$_3$-), 47,27 (H$_3$C-**C**H-CH$_3$); MS (EI) m/z (%)= 267 (100); IR (KBr pill) 2969, 2863, 2758, 2721, 2568, 2477, 2416, 2097, 1587, 1467, 1399,1204, 1151, 997, 664, 626, 565, 527, 472.

Preparation of bis(N,N-dimethylamino)chlorophosphine (**100**):

Hexamethylphosphorous triamine (**101**) (5,0 g, 30,6 mmol) was added dropwise to PCl_3 (2,1 g, 15,3 mmol), with stirring. After the exothermic reaction has finished, the mixture was heated at 100°C for 30 minutes. Vacuum distillation (p = 18 mbar, bp 67°C) afforded 6,2 g of yellow oil, a mixture containing bis(*N*,*N*-dimethylamino)chlorophosphine (**100**) and several uncharacterised side products.

Attempt for preparation of bis(diethylamino)chlorophosphine oxide (**102**):

Bis(N,N-diethylamino)chlorophosphine (**78**) (1,0 g, 4,76 mmol) was added to 7 ml dry CH_2Cl_2 and the solution was cooled to –18°C. *m*-CPBA (1,88 g 57-86%, 7,14 mmol) was dissolved in 10 ml dry CH_2Cl_2 and added dropwise to the reaction mixture. The clear solution was stirred at room temperature for 4 days. White precipitate was filtered off and the organic solution was washed with saturated $NaHCO_3$ solution and brine. The layers were separated and the organic layer was dried over $MgSO_4$ and evaporated to yield 650 mg of yellow oil. NMR data of this oil did not correspondent to literature data published for bis(N,N-diethylamino)chlorophosphine oxide.

Attempt for preparation of (tetraethyl)phosphorodiamidous acid-(2-ethyl) phenyl ester (**86b**):

Raw compound (**102**) (300 mg, 1,00 mmol) was dissolved in 5 ml CH_2Cl_2 and the solution was cooled to –18°C. A solution of *m*-CPBA (400 mg *m*-CPBA 57-86%, 1,5 mmol) in 5 ml CH_2Cl_2 was added dropwise. The mixture was stirred overnight at room temperature, TLC sample showed no starting material. The reaction mixture was washed with 5 ml saturated $NaHCO_3$ solution and 5 ml brine. The organic layer was dried over $MgSO_4$ and solvent was evaporated. The obtained oil (400 mg) was purified by silica gel column chromatography using petrolether : ethylacetat = 10:1 with 0,5% Et_3N as eluent. 250 mg of colourless oil were obtained (79% yield). The NMR and MS spectra of this compound did not correspond to the ones expected for the compound **86b**.

Preparation of *ortho*-ethyl N,N,N′,N′-tetraisopropylphosphorodiamidite (**112**):

Raw compound (**86c**) (300 mg, 0,85 mmol) was dissolved in 5 ml CH_2Cl_2 and the solution was cooled to –18°C. Solution of *m*-CPBA (350 mg *m*-CPBA 57-86%, 1,3 mmol) in 5 ml CH_2Cl_2 was added dropwise. The mixture was stirred overnight at room temperature, TLC sample showed no starting material. The reaction mixture was washed with 5 ml saturated $NaHCO_3$ solution and 5 ml brine. The organic layer was dried over $MgSO_4$ and

solvent was evaporated. The obtained crystals (320 mg) were purified by silica gel column chromatography using petrolether : ethylacetat = 10:1 with 0,5% Et_3N as eluent. 163 mg of colourless crystals were obtained (52% yield).

^{1}H NMR ($CDCl_3$): (δ) d 1,12 12H (**H**$_3$C-CH-C**H**$_3$), t 1,19 3H (C**H**$_3$-CH$_2$-), d 1,26 12H (**H**$_3$C-CH-C**H**$_3$), q 2,67 2H (CH$_3$-C**H**$_2$-), m 3,43-3,58 4H (H$_3$C-C**H**-CH$_3$), m 7,00-7,19 4H 3 (Ar**H**) d 8,08 1H (Ar**H**); ^{13}C NMR ($CDCl_3$): (δ) 22,24, 23,06, 46,02, 106,04, 119,9, 123,2, 126,6, 128,8, 129,81

Typical procedure for the metallation reaction with *s*BuLi :

Solution of bis(*N*,*N*-dialkylamino) phosphorodiamidous acid-(2-ethyl) phenyl ester (**86a-c**) or bis(*N*,*N*-dialkylamino) phosphorodiamidic acid-(2-ethyl) phenyl ester (**88a-b, 57a**) (1 eq) in 10 ml of dry THF was cooled to –105°C under argon atmosphere. TMEDA (1,2 eq) and *s*BuLi (1,2 eq) were added dropwise to the reaction mixture. After stirring for 1 hour at –105°C, solution of benzaldehyde (1 eq) in 10 ml dry THF was added dropwise. The mixture was stirred for an additional hour at –105°C, the reaction was then quenched with saturated NH_4Cl solution and allowed to warm up to room temperature. Organic compounds were extracted with CH_2Cl_2, the organic layer was dried over $MgSO_4$ and the solvent was evaporated to give a raw product. NMR spectrums of such raw samples showed that desired products were not formed.

Preparation of palladium catalysts:

[Pd((*R*)BINAP)][Cl]$_2$ was prepared in the reaction between Pd(COD)Cl$_2$ and (*R*)-BINAP in CH_2Cl_2 for 20 min at room temperature. The solvent and ligand COD were removed on the evaporator, and the product was used directly in the cyclisation reaction.

Preparation of palladium-dibenzylideneacetone complex Pd(dba)$_2$:

Sodium acetate (0,66 g, 7,9 mmol) was added to the hot methanolic solution (60°C) of sodium chloropalladite (0,78 g, 2,63 mmol) and an excess of dibenzylidenacetone (1,85 g, 7,9 mmol) (ratio dba : Pd ≥3). The mixture was allowed to cool to room temperature with stirring within 60 minutes. A brownish crystalline complex Pd(dba)$_2$ precipitated, The reaction mixture was filtered and the solid washed with water and acetone. The Pd(dba)$_2$ compound was obtained in almost quantitative yield of 1,51g (99% yield) m.p.135° (decomp.)

The $Pd(dba)_2$ complex obtained in this way was recrystallised from $CHCl_3$ or toluene to obtain $Pd_2(dba)_3 \cdot CHCl_3$ and $Pd_2(dba)_3 \cdot$toluene complexes, respectively. Thus the obtained $Pd_2(dba)_3 \cdot CHCl_3$ showed the same catalytic activity as commertially available compound.

Preparation of *trans*-Di(μ-acetato)-bis[o-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (**149**) (Herrmann catalyst):[95]

$Pd(OAc)_2$ (81 mg, 0,36 mmol) was dissolved in 9 ml toluene and $(o\text{-Tol})_3P$ (145 mg, 0,48 mmol) was added. The reaction flask was kept at 50° for 5 minutes and than cooled to room temperature. Mixture was concentrated to ¼ of the original volume under reduced pressure. 9 ml n-hexan was added; the precipitate was filtered and dried under vacuum. After recrystallisation from toluol/*n*-hexane, 124 mg of yellow powder were obtained (yield 78%).

Preparation of $Pd(PPh_3)_2Cl_2$:

885 mg $PdCl_2$ (5 mmol) and 425 mg LiCl (10 mmol) were dissolved in 7,5 ml dry MeOH and then Ph_3P (2,75 g, 10,5 mmol) was added. The mixture was heated at 50° under N_2 until a yellow precipitate was formed (1h). After cooling to room temperature, the reaction mixture was filtered and washed with 3 ml MeOH. The product was dried on air and recrystalised from *n*-hexane. Light-yellow crystals (3,06g, 83% yield) were obtained, m.p. >250°C.

The same general procedure was used for preparation of $Pd(P(o\text{-Tol})_3)_2Cl_2$:

885 mg $PdCl_2$ (5 mmol) and 425 mg LiCl (10 mmol) were dissolved in 7,5 ml dry MeOH and $(o\text{-Tol})_3P$ (3,19 g, 10,5 mmol) was added. The reaction mixture was heated at 50° under N_2 until a dark yellow precipitate was formed (1h) and then cooled to room temperature, filtered and washed with 3 ml MeOH. The product was dried on air and recrystalised from *n*-hexane. Orange-yellow crystals (4,12g, 99% yield) were obtained. m.p. >200°C.

Preparation of 2-Bromo-4-(5,5-dimethyl-[1,3]dioxan-2-yl)-6-methoxy-phenol (**150**):

300 ml of benzene were added to 2,0 g bromovanilline (8,66 mmol) 2,2-dimethylpropanediol (4,27g, 41,1 mmol) and *p*-TsOH (0,284g, 1,65 mmol). The reaction mixture was heated under reflux with a Dean-Stark apparatus for 20h. The reaction mixture was poured onto 100 ml CH_2Cl_2 and 20 ml H_2O. The organic layer was washed with water (5x20 ml) and brine (30 ml) and dried over $MgSO_4$. The raw product was purified with silica gel chromatography using Hexan:EtOAc = 7:3 as eluent yielding 70 % of 2-Bromo-4-(5,5-dimethyl-[1,3]dioxan-2-yl)-6-methoxy-phenol (**150**).

^{1}H NMR: (δ) s 0,79 (3H, C**H**$_3$-C), s 1,28 (3H, C**H**$_3$-C), d 3,75 (2H, -O-C**H**$_2$-C), d 3,78 (2H, -O-C**H**$_2$-C), s 3,93 (3H, C**H**$_3$O-Ar), s 5,30 (1H, Ar-C**H**-O), s 5,92 (1H, -O**H**), s 6,99 (1H, Ar**H**), s 7,24 (1H, Ar**H**)

Preparation of 4-(5,5-Dimethyl-[1,3]dioxan-2-yl)-2-iodo-6-methoxy-phenol (**151**):

300 ml of benzene were added to 2,4 g iodovanilline (**126**) (8,66 mmol) 2,2-dimethylpropanediol (4,27g, 41,1 mmol) and *p*-TsOH (0,284g, 1,65 mmol). The mixture was heated under reflux with aDean-Stark apparatus for 20h. The reaction mixture was poured onto 100 ml CH_2Cl_2 and 20 ml H_2O. The organic layer was washed with water (5x20 ml) and brine (30 ml) and dried over $MgSO_4$. The raw product was purified with silica gel chromatography using Hexan:EtOAc = 7:3 as eluent yielding 80 % of 4-(5,5-Dimethyl-[1,3]dioxan-2-yl)-2-iodo-6-methoxy-phenol (**151**).

^{1}H NMR: (δ) s 0,80 (3H, C**H**$_3$-C), s 1,28 (3H, C**H**$_3$-C), d 3,63 (2H, -O-C**H**$_2$-C), d 3,72 (2H, -O-C**H**$_2$-C), s 3,92 (3H, C**H**$_3$O-Ar), s 5,28 (1H, Ar-C**H**-O), s 6,10 (1H, -O**H**), s 7,01 (1H, Ar**H**), s 7,43 (1H, Ar**H**); MS (EI) m/z (%)= 364 (80), 278 (100), 151 (36), 115 (36), 69 (60)

Preparation of 2-Iodo-6-methoxy-4-((E)-propenyl)-phenol (**153**):

General experimental procedure for preparation of phenylpropenes from benzaldehydes yielded 23 % of compound **153** starting from iodovanilline (**126**).

^{1}H NMR (δ): d 1,85 (3H, C**H**$_3$-CH=), s 3,87 (3H, C**H**$_3$O-), m 6,02-6,15 (2H, **H**O-, CH_3-C**H**=CH), d 6,22 (1H, -CH=C**H**-Ar), s 6,80 (1H, Ar**H**), s 7,24 (1H, Ar**H**)

Preparation of *cis*-cinnamic alcohol (**156**):

A solution of 21 ml ethanol and 1,1 ml 2N aqueous NaOH was added to $NaBH_4$ (883 mg, 23,3 mmol) at room temperature. After being stirred for 10 min, the mixture was filtered through a Celite pad. A portion (12 ml) of the filtrate was added dropwise to a suspension of $Ni(OAc)_2 \cdot 4H_2O$ (2,39 g, 9,60 mmol) in 226 ml ethanol under vigorous stirring and hydrogen atmosphere. 1,9 ml ethylenediamine (28,7 mmol) and 1-phenyl-1-propin-3-ol (**155**) (5,08 g, 38,4 mmol) in 102 ml ethanol were added to the reaction mixture. After stirring for 4 hours, the mixture was diluted with water and extracted with EtOAc. The extract was dried over Na_2SO_4 and concentrated. Silica gel chromatography of the residue (hexane: ethyl acetate = 8:2) gave pure *cis*-cinnamyl alcohol (**156**) (4,63g, 90%) as oil.

IR (neat): 3331, 3103, 3082, 3057, 3022, 2928, 2866, 1601, 1576, 1495, 1447, 1339, 1317, 1248, 1217, 1182, 1078, 1018, 947, 916, 800, 773, 700 cm^{-1}. ^{1}H NMR (δ) s 1,69 (1H, -O**H**),

dd 4,43 (2H, J=1,6 and 6,4 Hz), dt 5,87 (1H, J=6,4 and 11,7 Hz,), d 6,57 (1H, J=11,7 Hz,), m 7,19-7,38 (5H, Ar**H**).

General method for preparation of phenylpropenes:[117]

Solution of EtMgBr in THF (3M, 0,1 mol) was added dropwise to a solution of corresponding benzaldehyde derivative (0,02 mol) in dry THF at 0°, the mixture was stirred for 3 hours at room temperature, and the excess EtMgBr was destroyed with MeOH. The reaction mixture was diluted with water and extracted with ether. The organic extract was washed with water, dried over $MgSO_4$, filtered and concentrated under a reduced pressure. The crude alcohol was used without purification in the next step.

A solution of crude alcohol (0,02 mol) in 50 ml of dry toluene was treated with 4,8 g (0,03 mol) of anhydrous $CuSO_4$. The reaction mixture was heated under reflux for 2 hours. An inorganic material was filtered and washed with toluene. After the evaporation of the solvent, the residue was purified by silica gel column chromatography (elution with hexane: ethyl acetate = 2:1).

2,4,6-trimethylphenylpropene (**160**) was prepared according to general procedure in 56 % yield.

^{1}H NMR: (δ) d 1,96 3H (C**H**$_3$-CH=), s 2,33 9H (2 x C**H**$_3$-Ar), m 5,74 1H (Ar-CH=C**H**-), d 6,38 1H (Ar-C**H**=CH-), s 6,91 2H (Ar**H**); MS (EI) m/z (%)= 162 (16), 161 (100), 133 (32)

2,4,6-trimethoxyphenylpropene (**161**) was prepared according to the general procedure in 53 % yield.

^{1}H NMR: (δ) d 1,89 3H (C**H**$_3$-CH=), s 3,81 3H (C**H**$_3$O-), s 3,82 6H (2 x C**H**$_3$O-), s 6,13 2H (Ar**H**), m 6,40-6,53 2H (Ar-C**H**=C**H**-); MS (EI) m/z (%)= 209 (12), 208 (100), 179 (48), 121 (16)

2,5-dimethoxyphenylpropene (**162**) was prepared according to the general procedure in 30 % yield.

^{1}H NMR: (δ) d 1,89 3H (C**H**$_3$-CH=), s 3,77 3H (C**H**$_3$O-), s 3,79 3H (C**H**$_3$O-), m 6,17-6,25 1H (Ar-CH=C**H**-), m 6,65-6,96 3H (Ar**H**, Ar-C**H**=CH-), s 6,96 1H (Ar**H**); MS (EI) m/z (%)= 179 (15), 178 (100), 166 (80), 105 (60), 85 (50)

General procedure for the cycloaddition reaction with halovanillines:

Palladium catalysed formation of dihydrobenzofuran (**144**) was performed (if not stated otherwise) according to the following typical procedure:

Iodovanilline (**126**) (278 mg, 1,0 mmol), palladium source (10 mol%), ligand (20 mol%) tetradecan (internal standard for GC, 0,05 ml) Ag_2CO_3 (330 mg, 1,2 mmol) and anethole (126 mg, 1,2 mmol) were dissolved in DMF under argon; the reaction vessel was sealed with PTFE/Butylkauchuk septum and stirred under argon at 50°C. After 24 hours, the reaction mixture was poured into 20 ml H_2O, acidified to pH=1 with 5 % HCl and extracted with ethyl acetate. Purification with silica gel chromatography using toluol:ethylacetat = 20:1 yielded dihydrobenzofuran (**144**) and benzofuran side product (**145**).

7-Methoxy-2-(4-methoxy-phenyl)-3-methyl-2,3-dihydro-benzofuran -5-carbaldehyde (**144**):

^{1}H NMR: (δ) d 1,44 (3H, C**H**$_3$-C), m 3,54 (1H, CH_3-C**H**-Ar), s 3,81 (3H, C**H**$_3$O-Ar), s 3,94 (3H, C**H**$_3$O-Ar), d 5,28 (1H, Ar-C**H**-O), d 6,91 (2H, Ar**H**), m 7,33-7,36 (4H, Ar**H**), s 9,84 (1H, –C**H**O); ^{13}C NMR: (δ) 17,94, 44,85, 55,26, 56,06, 94,50, 111,89, 114,05, 119,97, 127,82, 131,42, 133,66, 144,91, 153,26, 159,95, 162,29, 190,50; MS (EI) m/z (%)= 299 (16), 298 (100), 133 (24), 121 (60) Elemental analysis: 72,47 % C, 6,08 % H (calculated); 72,51 % C, 6,04 % H (found)

7-Methoxy-2-(4-methoxy-phenyl)-3-methyl-benzofuran-5-carbaldehyde (**145**):

^{1}H NMR (δ): s 2,48 (3H –C**H**$_3$), s 3,88 (3H –OC**H**$_3$), s 4,08 (3H –OC**H**$_3$), m 7,00-7,75 (6H Ar-**H**), s 10,03 (1H –C**H**O); IR: 2999, 2959, 2839 (Ar-H), 1678 (Ar-CHO) 1511, 1259, 1141, 828 (Ar-H), 725 (H-C=C-); MS (EI) m/z (%)= 297 (16), 296 (100), 281 (24), 148 (24) Elemental analysis: 72,96 % C, 5,44 % H (calculated); 73,01 % C, 5,39 % H (found)

3-Hydroxymethyl-7-methoxy-2-phenyl-2,3-dihydro-benzofuran-5-carbaldehyde (**157**):

^{1}H NMR: (δ) q 3,71 (1H, C**H**-CH_2-OH), s 3,97 (3H, C**H**$_3$O-), d 4,00 (2H, HO-C**H**$_2$-CH), d 5,79 (1H, Ar-C**H**-O), m 7,71-7,42 (7H, Ar**H**), s 9,83 (1H, -C**H**O); IR (neat): 3349 (-OH) 3008, 2936 (2 bands)(-CH_2-), 2836, 1685 (-CHO), 1591, 1312 (-OH), 1145, 1145, 752, 702 (H-C=C-H); UV (maximum, λ nm, ABS): 213,4 nm (1,031), 238,2 nm (0,671), 293,0 nm (0,560)

8-Methoxy-2-[1-phenyl-meth-(Z)-ylidene]-2,3-dihydro-benzo[1,4]dioxine-6-carbaldehyde (**158**)

^{1}H NMR: (δ) s 4,10 (3H, C**H**$_3$O-Ar), s 5,03 (2H, O-C**H**$_2$-C=), m 7,37-7,57 (4H, Ar**H**, C=C**H**-Ar), m 7,85-7,88 (3H, Ar**H**), s 10,03 (1H, -C**H**O); ^{13}C NMR: (δ) 55,98, 56,66, 128,02, 129,27, 129,87, 162,73, 192,08; MS (EI) m/z (%)= 282 (100), 265 (76), 165 (36)

General method for extention of aldehyde side chain of dihydrobenzofuran derivatives:[117]

Dry THF was cooled to 0°C, 3M EtMgBr solution in THF (197 mg, 0,5 ml, 1,48 mmol) was added, and dihydrobenzofuran derivative (0,7 mmol) dissolved in THF was added dropwise. The reaction mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure and the raw product was used in the next reaction without purification. Raw alcohol (0,7 mmol) was dissolved in dry toluene, anhydrous $CuSO_4$ was added and the mixture was refluxed 2 hours under argon. Inorganic salts were filtered off and solvent was removed under reduced pressure.

7-Methoxy-2-(4-methoxy-phenyl)-3-methyl-5-((E)-propenyl)-2,3-dihydro-benzofuran (**189**):

^{1}H NMR: (δ) d 1,37 (3H, C**H**$_3$-CH-Ar), d 1,86 (3H, C**H**$_3$-CH=), m 3,43 (1H, CH_3-C**H**-Ar), s 3,79 (3H, C**H**$_3$O-Ar), s 3,88 (3H, C**H**$_3$O-Ar), d 5,13 (1H, Ar-C**H**-O), m 6,02-6,18 (1H, CH_3-C**H**=), d 6,32 (1H, CH=C**H**-Ar), d 6,76 (2H, Ar**H**), d 6,88 (2H, Ar**H**), d 7,35 (2H, Ar**H**)

General method for preparation of diazonium salts:

Arylamin (0,1 mol) was added to 45 ml 32 % aqueous HBF_4. The mixture was cooled to −5°C, and a solution of $NaNO_2$ (6,9 g, 0,1 mol) in 15 ml H_2O was added dropwise within 30 minutes. The precipitate (arenediazonium salt) was filtered, dried on vacuum and washed with cold mixture Et_2O:MeOH = 4:1.

2-Hydroxy-benzenediazonium tetraflouroborate salt (**168**) was prepared according to the general method, after washing with Et_2O:MeOH and drying 12,9 g of product (**168**) were obtained (62 % yield).

MS (EI) m/z (%)= 206 (4), 120 (44), 112 (20), 92 (88), 64 (100)

5-chloro-2-Hydroxy-benzenediazonium tetraflouroborate salt (**170**) was prepared according to general method in 60 % yield, 14,5 g were obtained.

MS (EI) m/z (%)= 156(8), 154 (40), 126 (64), 98 (60), 63 (100)

The palladium catalysed cyclisation reactions with diazonium compounds were performed according to typical procedure for the cyclisation reaction with halogenoarenes. The GC yields were estimated using tetradecan as the internal standard. Some GC yields were checked and confirmed by isolating the product after silica gel chromatography using *n*-hexan:ethylacetat = 10:1 as the eluent.

2-(4-Methoxy-phenyl)-3-methyl-2,3-dihydro-benzofuran (**169**):

2-Hydroxy-benzenediazonium tetraflouroborate (**168**) (104 mg, 0,5 mmol), 10 mol % $Pd_2(dba)_3 \cdot CHCl_3$ (52 mg, 0,05 mmol) tetradecan (internal standard for GC, 0,05 ml), $CaCO_3$ (150 mg 1,5 mmol) and anethole (88 mg, 0,6 mmol) were mixed in CH_3CN under argon; reaction vessel was sealed with PTFE/Butylkauchuk septum and stirred under argon at room temperature. After the reaction was finished, the reaction mixture was poured into 2 ml unsaturated $NaHCO_3$ solution, and extracted with 2 ml ethyl acetate. The ethyl acetate was evaporated and a yellowish oil was obtained. Purification with silica gel chromatography using toluol:ethylacetat = 20:1 yielded 84 mg of dihydrobenzofuran (**169**) (70 % yield) as colourless oil.

^{1}H NMR: (δ) d 1,39 (3H, C**H**$_3$-C), m 3,43 (1H, CH_3-C**H**-Ar), s 3,80 (3H, C**H**$_3$O-Ar), d 5,10 (1H, Ar-C**H**-O), m 7,33-7,36 (8H, Ar**H**); MS(EI) m/z (%)= 240 (100), 225 (20), 209(15), 121 (30)

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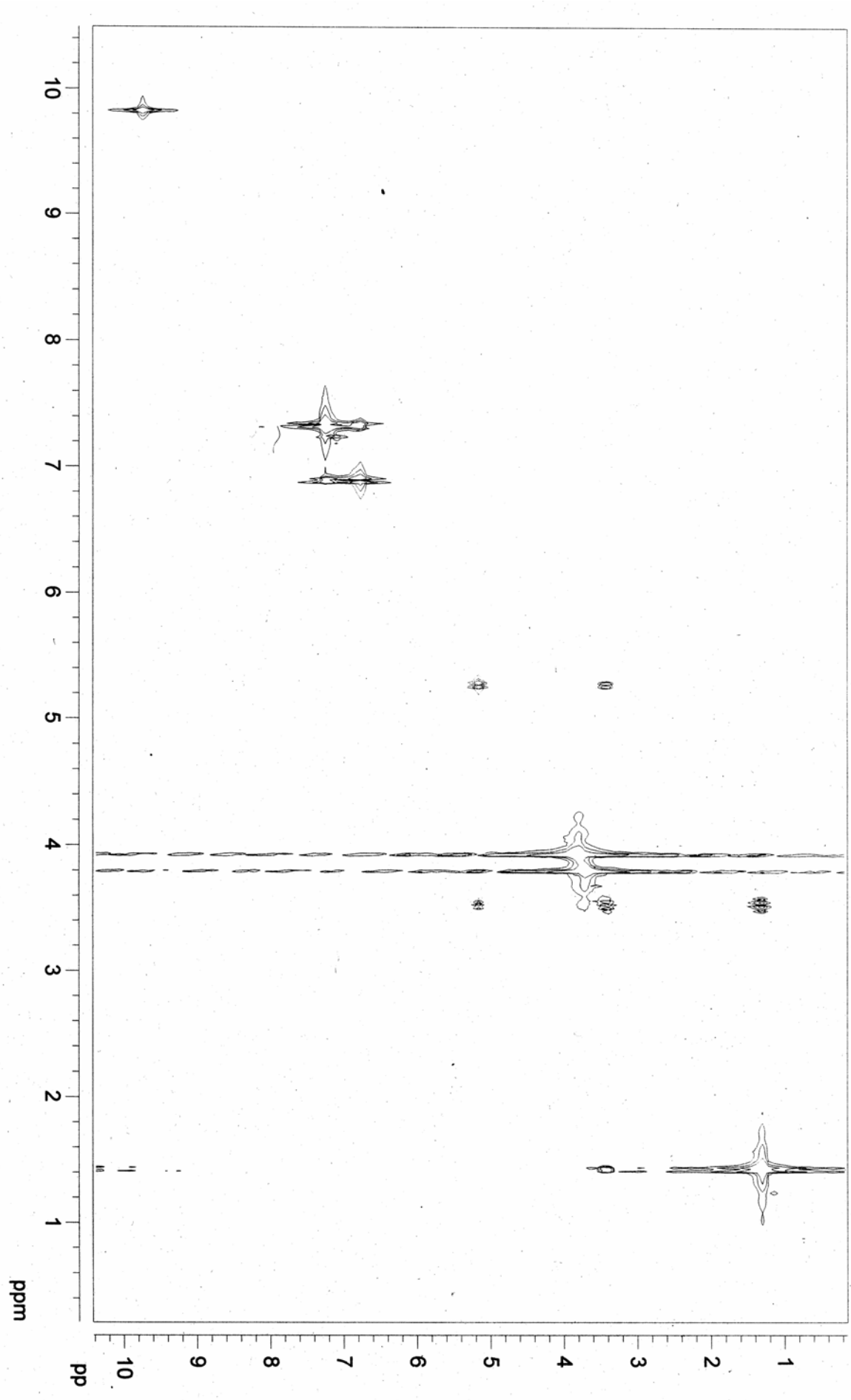
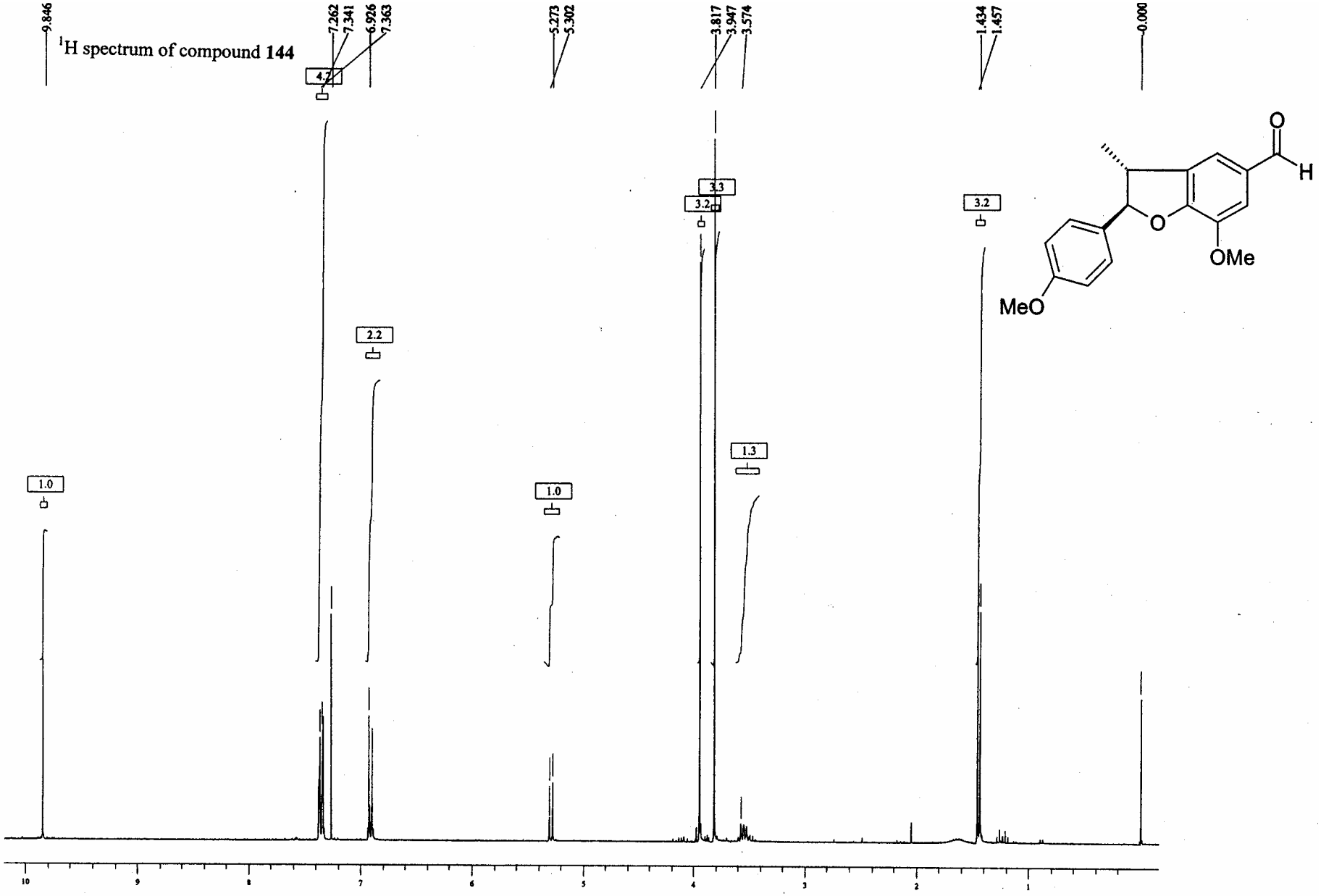
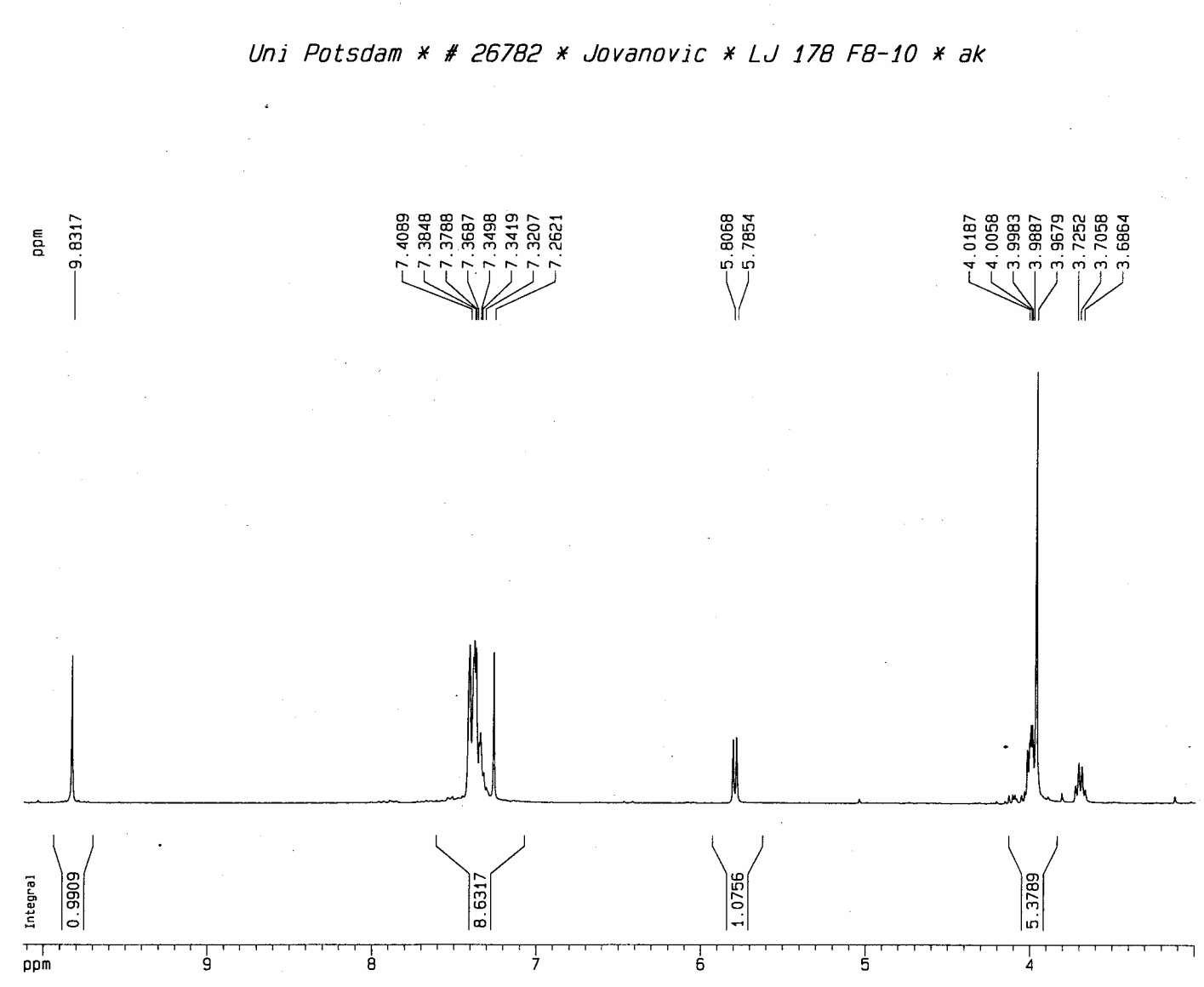


C-H COSY- spectrum of compound **144**

^{1}H spectrum of compound **144**





Current Data Parameters

NAME	ak.1h
EXPNO	4541
PROCNO	1

F2 - Acquisition Parameters

Date_	1011017
Time	8.10
INSTRUM	arx300
PROBHD	5 mm Multinu
PULPROG	zg
TD	16384
SOLVENT	CDCl3
NS	20
DS	0
SWH	7575.758 Hz
FIDRES	0.462388 Hz
AQ	1.0813940 sec
RG	64
DW	66.000 usec
DE	82.50 usec
TE	333.0 K
D1	1.00000000 sec
P1	4.00 usec
DE	82.50 usec
SFO1	300.1365179 MHz
NUCLEUS	1H

F2 - Processing parameters

SI	32768
SF	300.1333668 MHz
WDW	EM
SSB	0
LB	0.80 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	21.60 cm
F1P	10.121 ppm
F1	3037.72 Hz
F2P	3.000 ppm
F2	900.40 Hz
PPMCM	0.32969 ppm/cm
HZCM	98.95016 Hz/cm

^{1}H spectrum of compound **157**