Catalytic allylation of phenols : chloride-free route towards epoxy resins

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Catalytic allylation of phenols

Chloride-free route towards epoxy resins

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'dove la Natura finisce di produrre le sue spezie, l'uomo quivi comincia con le cose naturali, con l'aiutorio di essa Natura, a creare infinite spezie.'

Wanneer de natuur eindigt met het produceren van zijn eigen soorten, begint de mens, met natuurlijke zaken en de hulp van deze natuur, om een oneindigheid van soorten te creëren.

Leonardo da Vinci (1452-1519)

Table of contents

List of abbrevations

2,2-dppp	2,2-bis(diphenylphosphino)propane
2,2-dpp	2,2-diphosphinopropane
2,3-dppb	2,3-bis(diphenylphosphino)butane
2,4-dpppt	2,4-bis(diphenylphosphino)pentane
Ac	acetyl
An	anisyl
Ar	aromatic
binap	2,2'-bis(diphenylphosphino)-1,1'-binaphtyl
BPA	Bisphenol A
Bu	butyl
cod	1,5-cyclooctadiene
Cp	η^5-cyclopentadienyl
Cp*	η^5-pentamethylcyclopentadienyl
CP MAS	Cross Polarization Magic Angle Spinning
DVB	1,4-divinylbenzene
CSD	Cambridge Structural Database
Cy	cyclohexyl
DAE	diallyl ether
dba	dibenzylideneacetone
dcpe	1,2-bis(dicyclohexylphosphino)ethane
DEAD	diethylazodicarboxylate
DFT	density functional theory
dmdpp	2,2-dimethyl-1,3-diphosphinopropane
dmpp	1,3-bis(dimethylphosphino)propane
dpb	1,4-diphosphinobutane
dpe	1,2-diphosphinoethane
dpm	diphosphinomethane
dpp	1,3-diphosphinopropane
dppb	1,4-bis(diphenylphosphino)butane
dppdep	2,2-diethyl-1,3-bis(diphenylphosphino)propane
dppdmp	2,2-dimethyl-1,3-bis(diphenylphosphino)propane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppib	(diphenylphosphino)isobutene
dppm	bis(diphenylphosphino)methane
dppp	1,3-bis(diphenylphosphino)propane
dpppe	bis(2-diphenylphosphinophenyl) ether
dpptms	α,α'-bis(diphenylphosphino)tetramethylsilane
dtbpe	1,2-bis(di-*tert*-butylphosphino)ethane
dtbpp	1,3-bis(di-*tert*-butylphosphino)propane
ECH	epichlorohydrin (= 2-[chloromethyl]oxirane)
Et	ethyl

GC	gas chromatography
gem	*geminal*
h	hour(s)
HPLC	high performance liquid chromatography
ICP-AES	inductively coupled plasma atomic emission spectrometry
Me	methyl
MS	mass spectrometry
NMR	nuclear magnetic resonance
o	*ortho*
o-EtOdppe	1,2-bis(di-*o*-ethoxyphenylphosphino)ethane
o-Medppp	1,3-bis(di-*o*-methylphenylphosphino)propane
o-MeOdppdmp	1,3-bis(di-*o*-methoxyphenylphosphino)-2,2-dimethylpropane
o-MeOdppe	1,2-bis(di-*o*-methoxyphenylphosphino)ethane
o-MeOdppm	bis(di-*o*-methoxyphenylphosphino)methane
o-MeOdppp	1,3-bis(di-*o*-methoxyphenylphosphino)propane
OTs	*para*-toluenesulfonate
p	*para*
PES	potential energy surface
Ph	phenyl
p-MeOdppp	1,3-bis(di-*p*-methoxyphenylphosphino)propane
PP	bidentate phosphine ligand
PPh_3	triphenylphosphine
ppm	parts per million
Pr	propyl
tert	tertiary
THF	tetrahydrofuran
TMS	tetramethylsilane
TOF	turnover frequency (definition: mol of product formed per mol of catalyst precursor per hour)
tol	tolyl
TON	turnover number (definition: maximum formed mol of product per mol of catalyst precursor)
xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

1

General introduction

Abstract
The chemistry of the allylation reaction is reviewed and discussed. A new chloride-and salt-free route towards epoxy resin components is proposed. Multiple allylation reactions are discussed with an emphasis on allylations of phenols or/and with allyl alcohol as the allylating agent. A short introduction into phosphine ligand chemistry is given, followed by a description of the contents of this thesis.

1.1 Chloride- and salt-free route towards epoxy resins

1.1.1 Epoxy resins

Epoxy resins are among the most important industrial non-vinyl polymers and are used in large quantities in the production of glues, paints and coatings.[1] These polymers consist of monomers, of which the largest producer currently is Hexion Specialty Chemicals (formerly Resolution Performance Products) with an estimated production of 400 ktonnes a year, followed by The Dow Chemical Company and Huntsman (formerly Vantico) in second and third place (estimated production in 2005). Bisphenol A (Figure 1.1a), synthesized from phenol and acetone in the presence of acid,[2,3] is the core substrate in the production of epoxy resins. The main monomer used in the epoxy resin industry is the diglycidyl ether of bisphenol A that represents more than 75% of the resin used in industrial applications (Figure 1.1b).[4] In the structure shown in Figure 1.1c, n represents the number of times the repeating unit occurs in the prepolymer. If n is 0 (most commonly used; Figure 1.1b) or 1, the product is a viscous liquid. If n is greater than 1 the product is a brittle solid. The epoxide group at the terminal positions of these molecules serves as the reactive site for crosslinking in thermoset

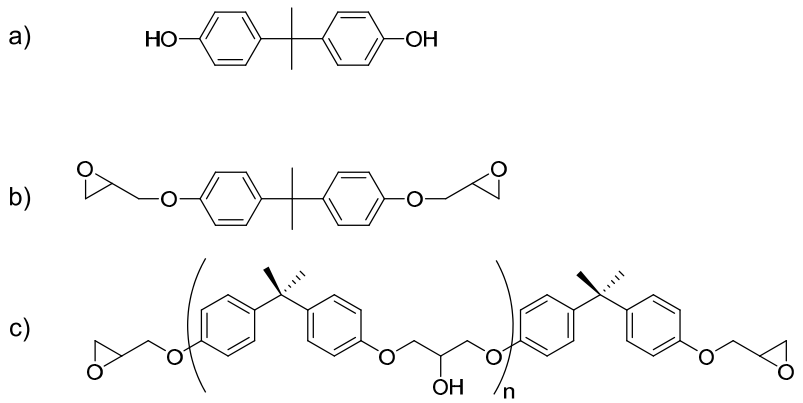
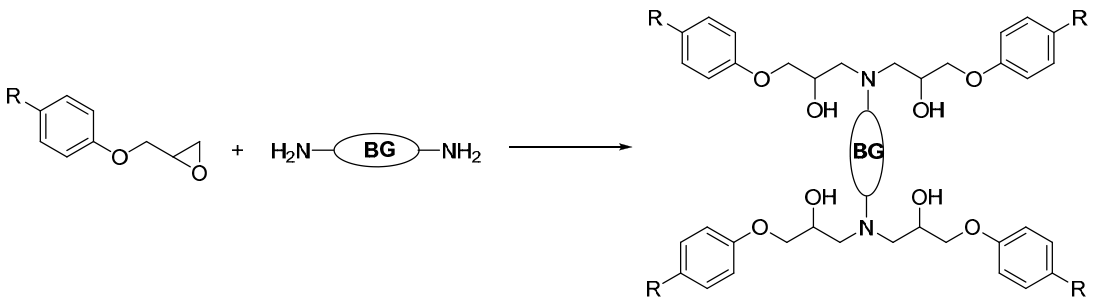


Figure 1.1. General structure of a) bisphenol A b) structure of diglycidyl ether of bisphenol A and c) general structure of diglycidyl ether of bisphenol A resin.



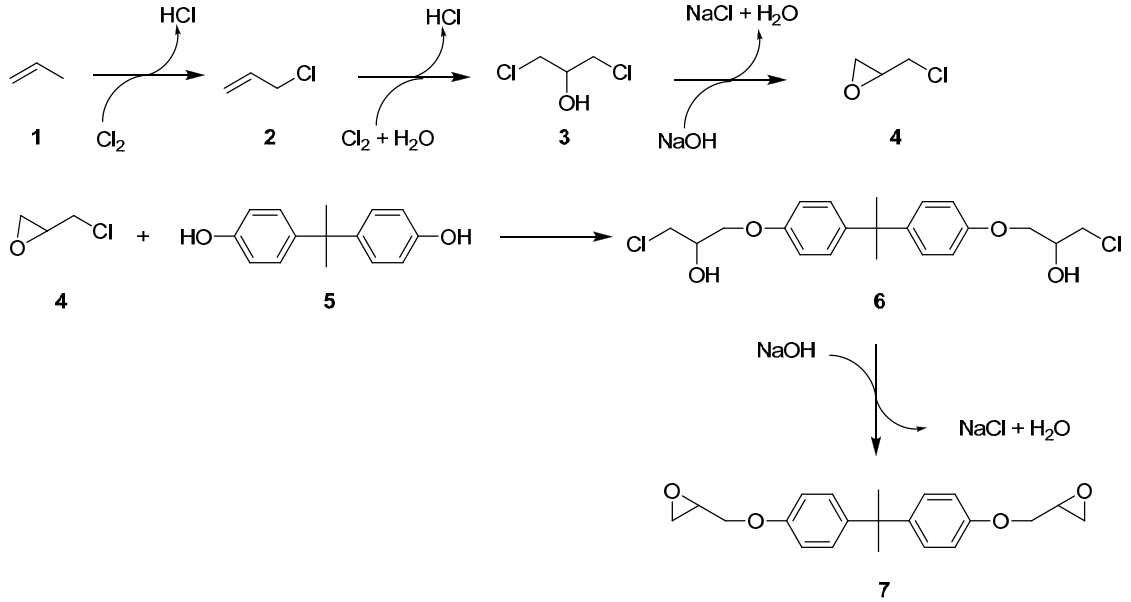
Scheme 1.1. Curing mechanism for epoxy resins (BG = bridging group).

polymers. The chemical chosen to react with these epoxides is referred to as the curing agent, and it typically has reactive hydrogens attached to nitrogen, oxygen, or sulfur.[4,5] Amine curing agents are the most common and can be primary or secondary, aliphatic or aromatic, or cycloaliphatic. The amines typically have more than three reactive sites per molecule that facilitate the formation of a three-dimensional polymer network when mixed with the epoxy resin (Scheme 1.1).

1.1.2 Current process for synthesis of diglycidyl ether of bisphenol A

The production of the diglycidyl ether of bisphenol A used today starts with the synthesis of epichlorohydrin (ECH) (Scheme 1.2).[6] To obtain this key reagent, propene (**1**) is reacted with chlorine gas to form allyl chloride (**2**), which is then further reacted with steam and again chlorine gas to obtain 1,3-dichloropropan-2-ol (**3**).[7] This step is however very inefficient, since also a large amount of trichloropropane is produced and a very large excess of water is required to obtain a reasonable yield for **3**. Finally, ECH (**4**) is formed by adding hydroxide as a base to compound **3**. The ECH is then reacted with bisphenol-A (**5**) into a 'chlorohydrin ether' **6** which is dehydrochlorinated using again hydroxide to form the desired epoxide **7**.[6] The relative amounts of the reactants determine the value of *n* in Figure 1.1 and a large excess of epichlorohydrin over BPA favors the formation of $n = 0$.

As indicated, this production process is based on stoichiometric salt chemistry and gives larges quantities of inorganic and organic chlorides, both in the formation of the intermediate

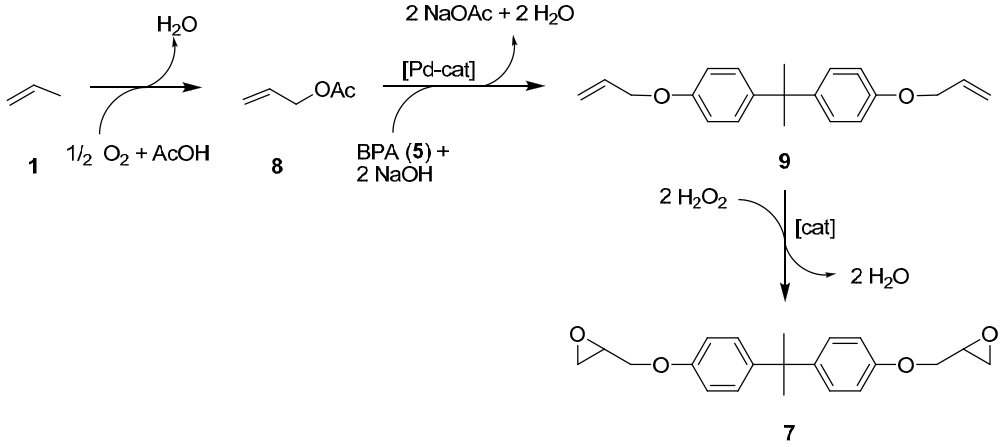


Scheme 1.2. Current process towards bisphenyl A diglycidyl ether.

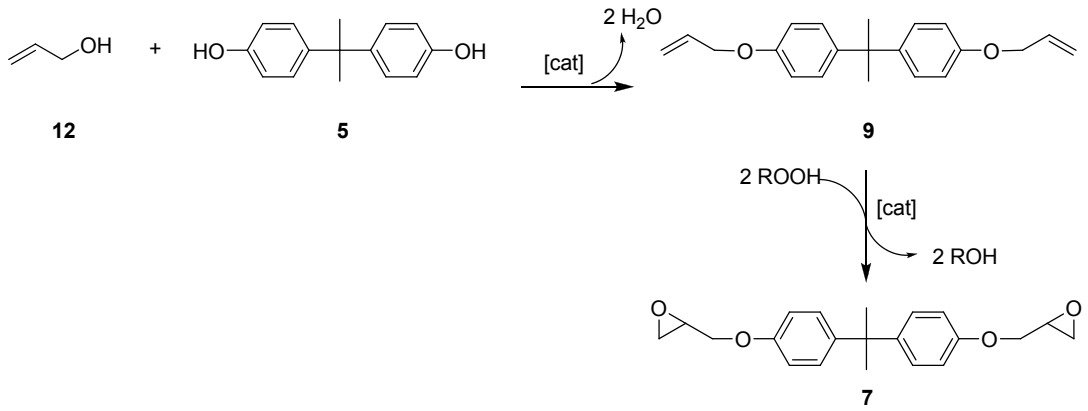
allyl chloride and epichlorohydrin, as well as in the formation of the final product. Large excess water is needed to minimize byproduct formation which makes the process energy intensive in order to separate ECH from the large water stream. A different process which is much less energy intensive and has a much higher atom efficiency will help both economically and environmentally.

1.1.3 Alternative routes

An alternative route towards **7** has been patented by Dow Chemicals (Scheme 1.3),[8] which makes use of allyl acetate as allylating agent in a palladium-catalyzed formation of the bisallyl ether of bisphenol A. In this route, however, still stoichiometric amounts of acetate salts are formed as by-products, although the desired bisallyl ether product was formed in high yield and with high selectivity. The catalyst used is a palladium(0) triphenylphosphine complex with a turnover frequency of 12,800 h^{-1}. Another problem in this route is the epoxidation of the diallyl ether to the desired bisglycidyl ether, because the reported catalyst has a low selectivity and activity and a suitable catalyst has not been found yet for this step. Other patents mention the allylation towards **9**, either without a catalyst and the use of allyl halides and base,[9] or with a catalyst, based on ruthenium or palladium, using allyl acetate as the allylating agent.[10]



Scheme 1.3. Proposed chlorine free alternative route towards bisphenyl A diglycidyl ether as proposed by Dow Chemicals.

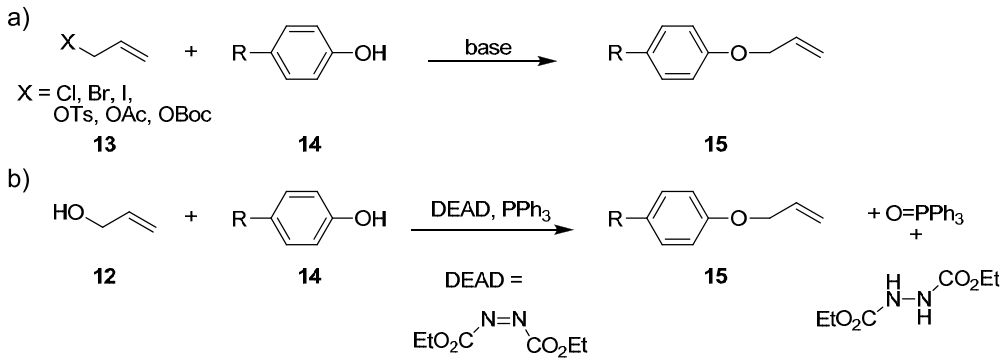


Scheme 1.4. Proposed chlorine-free and salt-free process towards bisphenyl A diglycidyl ether (**7**).

In Scheme 1.4 is shown a chlorine- as well as salt-free route via the direct nucleophilic substitution of allyl alcohol. This would be a revolutionary development in the synthesis of epoxy resins. Allyl alcohol is a cheap and easily accessible starting material and only water is produced as a byproduct in the first step of this route. When the formed bisallyl ether can be effectively epoxidized, the desired product is formed in only two steps. The ultimate challenge lies in finding suitable catalysts for the selective formation of the bisallyl ether of BPA and its subsequent selective catalytic epoxidation to BPA diglycidyl ether that can be used in a commercial chloride-free process for the synthesis of epoxy resins. The study of the allylation step is the main focus of this thesis.

1.1.4 Other uses for the catalytic allylation reaction

An efficient catalyst for the synthesis of allyl ethers can be employed for more goals than only the production of epoxy resin components. Another important use of allylic ethers is as a protecting group for a hydroxyl functionality. They are stable in both acidic and basic conditions and have a high removal potential by catalytic de-allylation processes. The allyl group as protecting group in carbohydrate chemistry has been reviewed by Guibe,[11] describing both the protection as well as the deprotection methods. In carbohydrate chemistry, practically only allyl halides and acetates are used and therefore the use of allyl alcohol as the allylating agent could give new possibilities in protecting group strategies. Besides carbohydrate chemistry, other biologically interesting molecules become accessible or their tedious and long syntheses can be shortened by introduction of this catalytic step. Not only allyl ethers are useful compounds, but also the C-allylated products can be of use, like *ortho*-allylphenol, which is used as an intermediate in the pharmaceutical industry, for example for producing compounds against androgenic disorders (skins problems).[12]



Scheme 1.5. Non-catalytic synthetic routes to allyl phenyl ethers.

1.2 Allyl ether formation

1.2.1 Non-catalytic methods

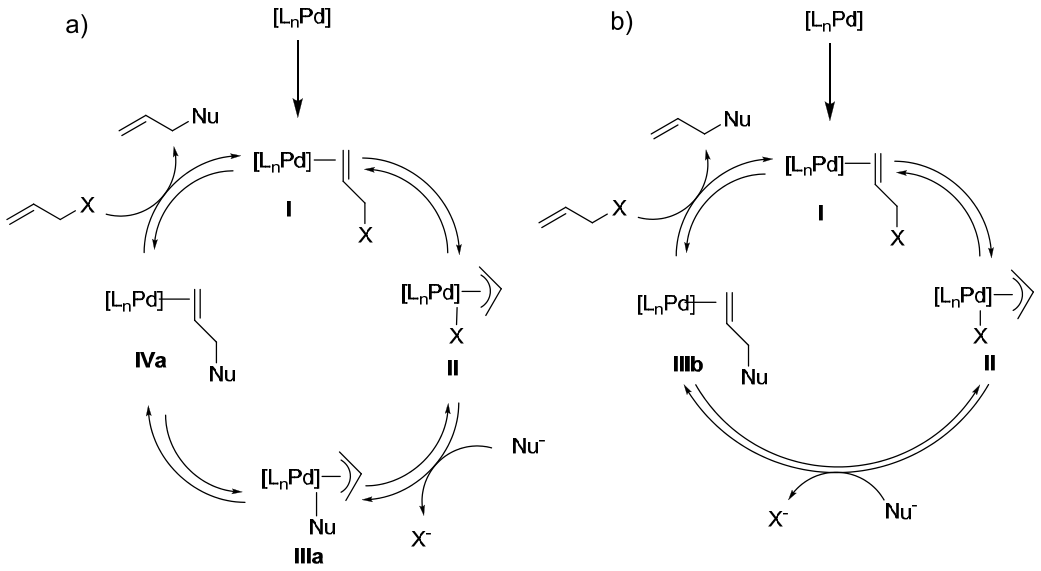
Classically, phenyl allyl ethers are obtained by the Williamson ether synthesis, in which allyl species with a good leaving group, such as halides, tosylates, carboxylates or carbonates (Scheme 1.5a), are reacted with a phenol under the agency of stoichiometric amounts of base.[13-16] Also Mitsunobu-type reactions can be used (Scheme 1.5b), where instead of an allyl substrate with a good leaving group, allyl alcohols can be used in combination with a stoichiometric amount of a coupling agent such as DEAD (= diethylazodicarboxylate), in combination with triphenylphosphine.[17-21]

Although these reaction have high yields and are easily performed, they would produce a stoichiometric amount of saline and organic waste and on an industrial scale, which is clearly undesired. A catalytic system does not have this major disadvantage.

1.2.2 Allylations reaction employing allyl donors with good leaving groups

Palladium catalysis

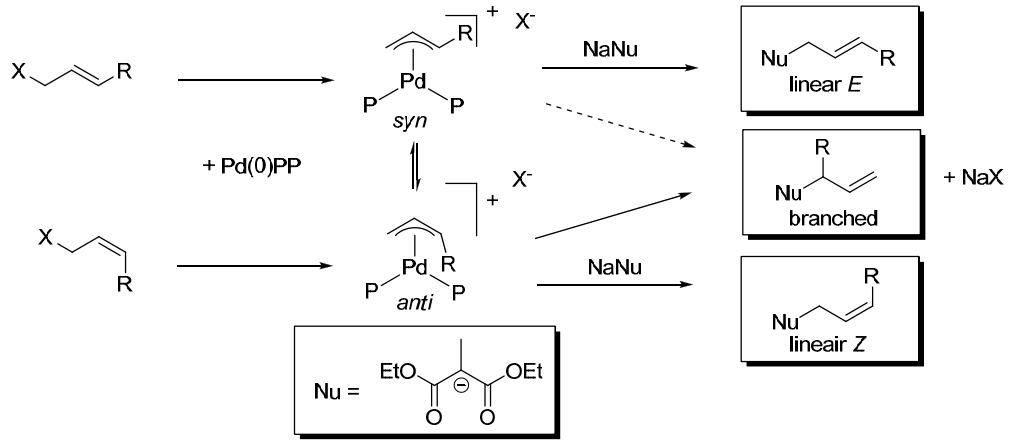
The allyl group is a highly used reactive group in organic chemistry and various types of catalytic allylation reaction have been reported. In most cases, allyl donor molecules are used with good leaving groups. A well-known allylation reaction is the palladium-catalyzed Tsuji-Trost allylic alkylation[22,23] where an allyl-X is reacted with a nucleophilic substrate such as active methylenes, amines, enolates and phenols. The X represents a good leaving group, like halides, carboxylates or carbonates. The reaction has been studied in great detail and has been the subject of several reviews.[24-27] The generally accepted mechanism is shown in Scheme 1.6.



Scheme 1.6. Proposed mechanism for the Tsuji-Trost type allylation reactions of a) hard nucleophiles and b) soft nucleophiles.[25]

Two different mechanisms are shown, which are governed by the nature of the nucleophile. After coordination of the allylating agent to the palladium(0) complex (**I**), oxidative addition takes place to form species **II**. For hard nucleophiles, such as Grignard reagents, alkylzinc halides and hydride donors, the mechanism shown in Scheme 1.6a applies, where the leaving group is replaced by the nucleophile, that coordinates onto the Pd(II) to form intermediate **IIIa**, after which reductive elimination takes place to form the palladium-bound allylated product (**IVa**). For soft nucleophiles, such as β-diketones, amines and amides, however (Scheme 1.6b), direct attack of the nucleophile on the allyl group is proposed, without prior coordination onto the palladium complex (**II** to **IIIb**).[25]

Many examples of this reaction are known and regioselective[29,30] and enantioselective[31,32] versions have been reported. Reaction with unsymmetrically substituted allyl substrates often give a substrate-dependent product distribution.[33-36] The allylation of (*E*)-substrates with Pd-



Scheme 1.7. Regioselective allylation of sodium diethyl 2-methylmalonate.[28]

complexes having bidentate phosphine ligands results in formation of the linear (*E*)-product and it has been reported that a larger bite angle of the ligand results in an increase of the regioselectivity (Scheme 1.7).[28] Analogously, the allylation of (*Z*)-substrates results in the formation of the linear (*Z*)-product. Remarkably, for (*Z*)-substrates, a larger bite angle of the ligand leads to an increased regioselectivity for the formation of the branched product instead of the linear product ligand.

Alcohols are also known to participate in allylic alkylations. Aliphatic alcohols are efficiently allylated with allyl acetate,[37] but addition of Et_2Zn is eminent for the reaction to proceed. Addition of stoichiometric amounts of reagents is often employed also for other types of substrates to generate a strong nucleophile. Not many examples have been reported where phenols are O-allylated with a palladium catalyst using allyl-X as the allylating agent. The patents discussed earlier describe the use of the Tsuji-Trost reaction to allylate phenols (among which BPA) with allyl acetate as the allylating agent.[8,10] Muzart *et al.* use KF and alumina to create a phenolate anion *in situ*, which is allylated with allyl acetates.[38]

Ruthenium catalysis

Ruthenium has often been reported to be a suitable metal for catalysts in Tsuji-Trost-type allylation reactions. The most commonly used ruthenium catalysts contain either a Cp or Cp* (Cp = cyclopentadienyl; Cp* = pentamethylcyclopentadienyl) ligand. The utilisation of [RuCp*Cl(cod)] (Figure 1.2; structure **I**) as a catalyst for the substitution of cinnamyl carbonate with piperidine results in high regioselectivity towards the branched products.[39] However, the regioselectivity for this catalyst is highly dependent on the nature of the substitution of the allyl substrate. For allylic substrates substituted with an aromatic group the selectivity is high, but for aliphatic substituents loss of selectivity is observed. $[RuCp(MeCN)_3](PF_6)$ and especially $[RuCp^*(MeCN)_3](PF_6)$ (**II**) are excellent catalysts for allylation reactions.[40] Bruneau and co-workers have reported the use of similar catalysts with nitrogen-donor ligands (**III**).[41-44] Pregosin and co-workers have reported the use of Ru(IV)

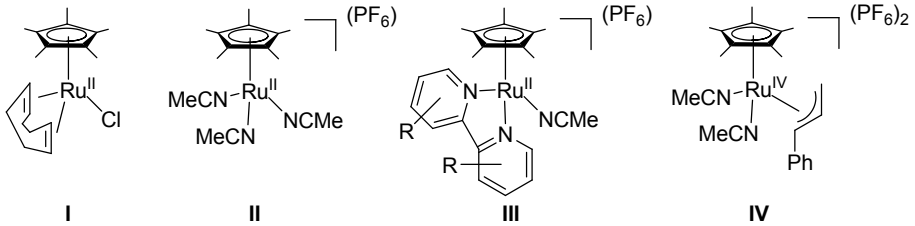
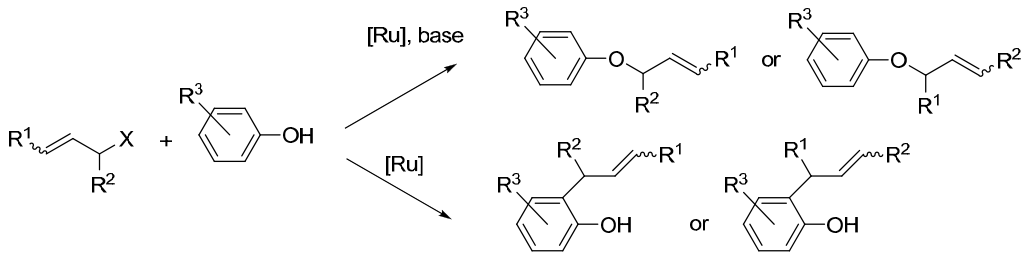


Figure 1.2. RuCp*- complexes used as catalysts for allylation reactions.

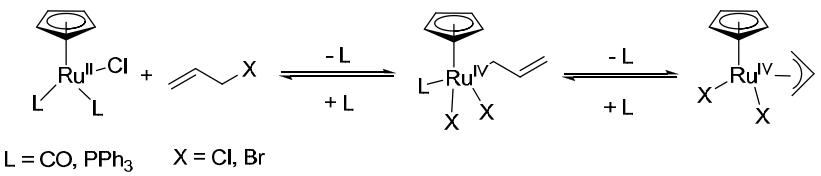


Scheme 1.8. O-and C-allylation of phenolic compounds in the presence of ruthenium catalysts.

complexes as pre-catalyst (**IV**)[45-47] for allylation reactions, entering the catalytic cycle of allylation reactions at a different point, namely after the oxidative addition step.

O-Allylation of phenols with a ruthenium catalyst has been reported using allyl halides as the allylating agent.[48,49] A stoichiometric amount or even an excess of base on the phenol is often added to induce reactivity of the phenol (Scheme 1.8) by forming a phenolate species *in situ*. The reaction proceeds efficiently and substituted allyl chlorides can be reacted with high regioselectivity. In the absence of base, phenols are reactive, however, instead of O-allylation, C-allylation takes place (Scheme 1.8). Apart from phenols other aromatic compounds can be allylated at the phenyl rings in a Friedel-Craft-type reaction.[50] A similar reaction was also reported for 2-pyridylarenes, using a Ru-catalyst.[51]

The mechanism of these Tsuji-Trost-type reactions is in general proposed to proceed via a π-allyl species, in analogy with the mechanism depicted in Scheme 1.6. However, σ-allyl species most likely also play a role in the mechanism and several reports on their existence have been published.[53-56] The presence of coordinating anions seems to be important in the formation of these Pd(σ-allyl) species. Apart from Pd-based systems, existence of σ-allyl species has also been proposed for Ru-based systems. It has been reported that when allyl chloride or bromide is reacted with $RuCp(CO)_2X$ or $RuCp(PPh_3)_2X$, σ-allyl species are initially observed using NMR spectroscopy, which react further into π-allyl species after dissociation of a ligand to form [$Ru(IV)X_2$(π-allyl)] (Scheme 1.9).[52] The reverse reaction is observed when excess of ligand is added to this Ru(IV) compound and reductive elimination takes place to regenerate the $RuCp(L_2)X$ complex.



L = CO, PPh_3 X = Cl, Br

Scheme 1.9. Proposed intermediates in the oxidative addition of allyl-X onto $RuCp(L_2)X$.[52]

Other metal-ions as catalysts for allylation reactions

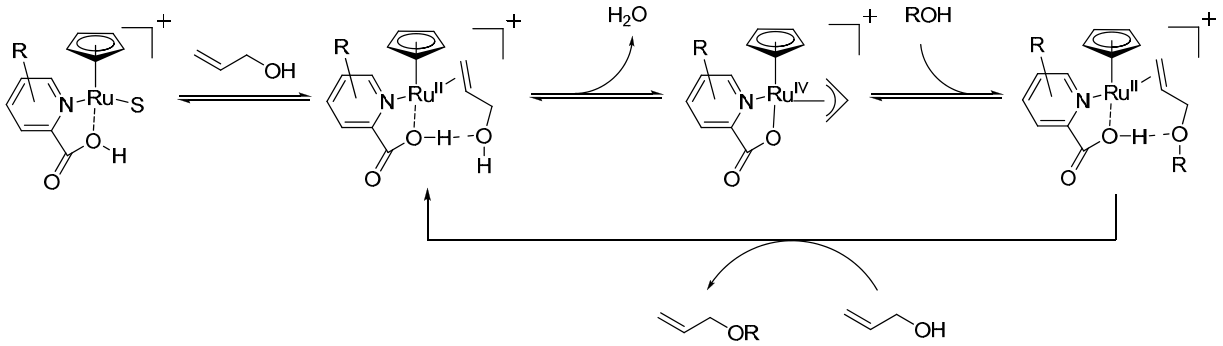
Apart from palladium- and ruthenium-based catalysts other transition metal complexes are known to catalyze allylation reactions. An iridium complex, $[Ir(cod)_2]BF_4$ has been reported to catalyze the reaction between aliphatic alcohols and allyl acetate to yield allyl alkyl ethers in quantitative yields.[57] Amines and phenoxides can also be allylated using a similar catalyst.[58,59] Molybdenum-based catalysts have been used in similar allylation reactions.[60] Also, a rhodium(I) catalyst has been reported to catalyze O-allylation of phenols with allyl carbonates in the presence of base.[61] Again, phenolate salts are produced in a stoichiometric amount to induce reactivity towards allyl ethers.

1.2.3 Allylation reactions with allyl alcohol as the allyl donor

Dehydrative allylation reactions

In the past decade, the concept of "sustainability" and "green chemistry" has become increasingly important. It would be much more attractive to use allyl alcohol as the allyl donor from an environmental and atom-efficiency point of view, as only water is co-produced. A major drawback when using allyl alcohol is that it shows a much lower tendency for nucleophilic substitution than the corresponding halide, carbonate or carboxylate derivatives, because of the poor leaving ability of hydroxide anion. Nonetheless, an increasing number of catalysts has been reported to effectively activate allyl alcohols for dehydrative allylation reactions.

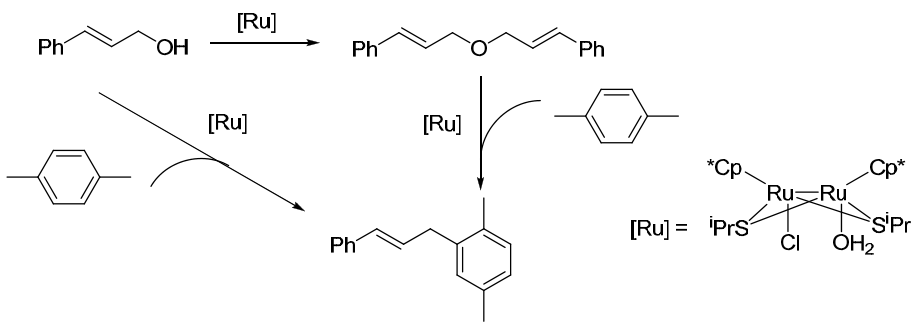
A Pd-triphenyl phosphite catalyst has been reported to show high activity for the allylation of aliphatic alcohols with various types of allyl alcohols.[62] Besides cross-allylations, also the reaction of allyl alcohol with itself is observed, forming diallyl ethers. Interestingly, no addition of stoichiometric amounts of base is needed to induce reactivity of the aliphatic alcohol. The base is generated *in situ*, because the hydroxide anion generated from the C-O bond cleavage of allyl alcohol facilitates the nucleophilic attack of the aliphatic alcohols. Similar reactions have been performed with both palladium(0)- or nickel(0)-phosphine complexes as catalyst,[63] which are also capable of allylating secondary amines. Nickel-based catalysts proved to be more efficient in coupling reactions of allyl alcohol with soft nucleophiles than their palladium counterparts. Allylic amination proceeds with higher TOF's (= turnover frequency) for nickel than for palladium, for identical bidentate phosphine ligands. With a ratio substrate/catalyst of 50/1 at a temperature of 80 °C, a TOF of 300 h^{-1} was reached for Ni, whereas for Pd only 125 h^{-1} is obtained. Palladium-xanthene-phosphole



Scheme 1.10. Proposed mechanism for Ru-catalyzed allylation of alcohols.[67]

complexes have been demonstrated to be effective catalysts for the allylation of aniline.[64] Besides aniline derivatives, also alkylamines can be allylated with allyl alcohol as the allylating agent using a Pt-catalyst with phosphine ligands having large bite angles.[65] N-heterocycles are successfully allylated with allylic alcohols employing palladium catalysts with phosphine ligands. The described catalysts have bidentate phosphine ligands, formed *in situ* from two monodentate fragments held together via hydrogen bridging.[66]

Saburi and co-workers have reported the ruthenium-catalysed ether formation of allyl alcohol with alcohols, employing a $[CpRu(MeCN)_3]PF_6$ complex with 2-quinolinecarboxylic acid as auxiliary ligand.[67] For aliphatic alcohols this catalyst was successful, but in the allylation of tertiary and aryl alcohols, the yields were poor and were ascribed to the lower nucleophilicity of the latter substrates and the reversibility of this catalysis. With a substrate to catalyst ratio of 10000, a TON (= turnover number) of 6500 and a TOF of 5200 h^{-1} at 26% conversion was reported in the reaction of aliphatic alcohols with allyl alcohol. To overcome the problem that allyl alcohol has a poor leaving group, an acidic residue is present on the ligand to protonate the hydroxyl group *in situ* and form water, which is a much better leaving group (Scheme 1.10). After the oxidative addition of allyl alcohol, a Ru(IV)(π-allyl) intermediate is formed, which was successfully isolated.[67] This intermediate subsequently reacts with an alcohol to



Scheme 1.11. Reactivity of allyl alcohols with aromatic compounds in the presence of thiolate-bridged diruthenium complexes.[68]

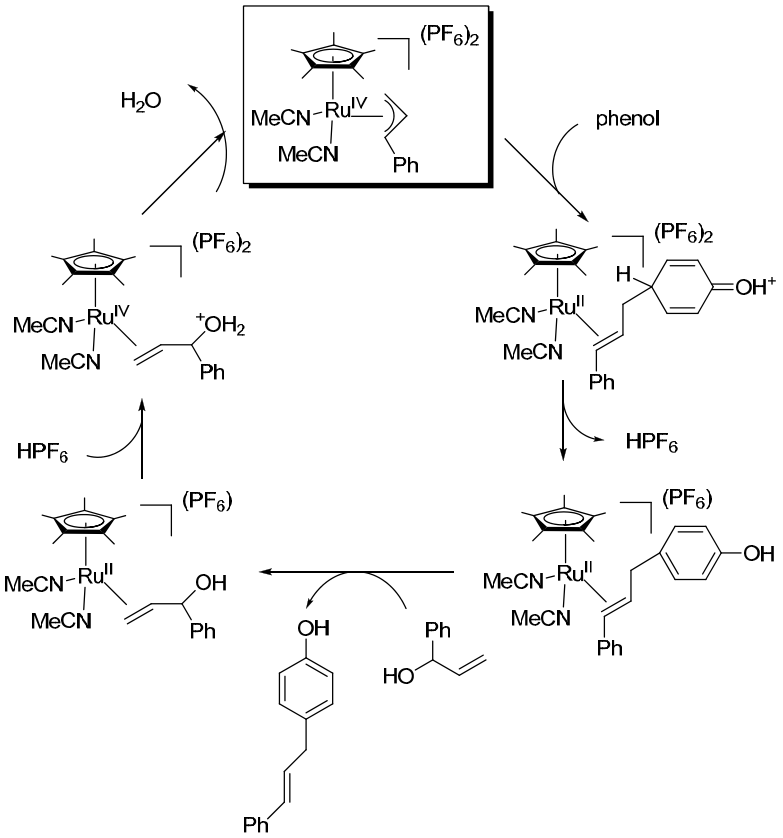
obtain a Ru(II) species coordinated to the allyl ether. After exchange of the product with a new molecule of allyl alcohol, the catalytic cycle is completed. Although all the elementary steps in the cycle are reversible, the phase separation of water from the reaction mixture and the low nucleophilicity of water is claimed to drive the equilibrium to the allyl ether side. In alcoholic solvent, however, the same complex has been reported to cleave allylic ethers to form the alcohols.[68]

Thiolate-bridged diruthenium(II, III) complexes have been shown to catalyze the allylation of aromatic compounds with allyl alcohols.[69] Besides compounds with phenyl rings, heterocyclic compounds such as thiophenes and furans can be allylated. In the beginning of the reaction, formation of diallyl ethers is observed, but these react further away to form the allyl substituted aromatic compound in high yield (Scheme 1.11)

Allylation of phenols with allyl alcohol

For the revolutionary proposed route towards epoxy resin (Scheme 1.4), O-allylation of phenols with allyl alcohol must be achieved. Thusfar, only a single example is known were allyl phenyl ethers are catalytically and selectively produced from a phenol and allyl alcohol,[70] however, a stoichiometric amount of base, in the form of $Ti(O\textit{i}Pr)_4$, needs to be added to induce O-allylation of phenols. It is also questionable wether allyl alcohol is the allylating agent or if allyl-titanoate species are formed. In the possible mechanism for the formation of allyl aryl ethers, allyl alcohol or an allyl-titanoate, formed by the exchange reaction between allyl alcohol and isopropoxide in $Ti(O\textit{i}Pr)_4$,[71] reacts with the Pd(0) species that is formed *in situ* to afford a π-allyl palladium species. The subsequent reaction with phenol followed by reductive elimination gives allyl aryl ether. Another function of the $Ti(O\textit{i}Pr)_4$ may be the acceleration of the reduction of $Pd(OAc)_2$ to a Pd(0) species as was observed in previous experiments by Satoh *et al.*[72]. The addition of this base should be circumvented, as it yields stoichiometric saline waste, but in the absence of such a base, a similar system exclusively yields C-allylated products.[73]

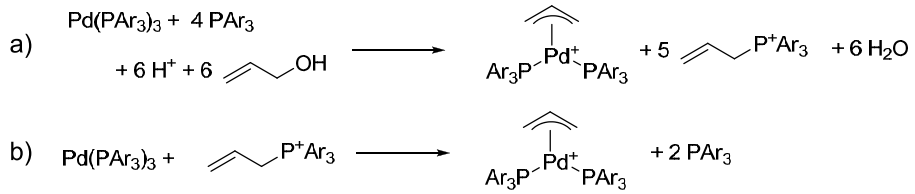
A ruthenium-based catalytic system has been reported to catalyze the allylation of phenols with allyl alcohol, but again, only C-allylated products are formed.[74] The catalyst precursor is a Ru(IV)Cp*(allyl) compound, which means that the catalytic cycle is entered after oxidative addition of the allyl alcohol compared to the cycle shown in Scheme 1.10, where the cycle is initiated before oxidative addition. A strong acid is generated *in situ* (HPF_6) as a co-catalyst to properly activate allyl alcohol. The mechanism proposed for this catalytic system is shown in Scheme 1.13 and resembles a Friedel-Craft-type reaction. Besides C-allylation of phenols,



Scheme 1.13. Proposed mechanism for Ru-catalyzed C-allylation of phenol with RuCp*$(MeCN)_2$-complex.[74]

other substrates can also be successfully allylated, like thiols,[75] pyroles and indoles[76,77] using a very similar catalytic system.

Kuntz *et al.* have described the allylation of phenols in water using a water soluble Pd-catalyst with sulfonated phosphines as ligands.[79] The relation between selectivity for either O- or C-allylation and the addition of base has been described, although very low yields are reported for the reactions in water. The system is compared to that in an organic solvent, which shows much higher conversion of the phenolic substrates. The behavior of these water-soluble Pd-catalysts at different pH in the presence of allyl alcohol was studied in detail[78] and it was found that free phosphines are rapidly converted into allyl phosphonium salts (Scheme 1.12a). A low pH (high acidity) of the reaction medium promotes oxidative addition of allyl alcohol and therefore the total reaction, but the presence of acid is not required for activity. At neutral



Scheme 1.12. Allylation of free phosphine with consumption of acid to form allyl phosphonium salts and water in the presence of a Pd(0) complex and b) the reverse reaction.[78]

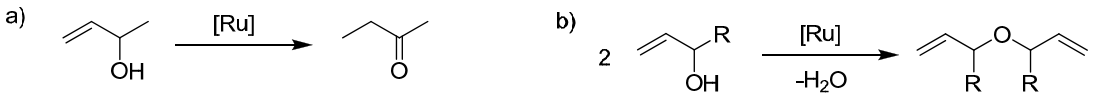
conditions without acid addition, hydroxide is formed and the pH of the medium slowly increases. Interestingly, only one of the initially coordinated phosphines reacts with allyl alcohol, but only because this phosphine is replaced by coordination of allyl alcohol onto the palladium catalyst and freely present in solution. The allyl phosphonium salts are formed reversibly, since they can undergo a oxidative addition reaction with a neutral Pd(0)-phosphine species (Scheme 1.12b), to obtain a palladium-allyl complex and free phosphine.

1.2.4 RuCp-complexes with phosphine ligands in allylation reactions

In an attempt to find a highly active catalyst for the isomerization reaction of allyl alcohols into carbonyl compounds in the presence of conjugated dienes,[80,81] van der Drift *et al.* investigated a series of $[RuCp(PP)]^+$ complexes for activity in the isomerization of 3-buten-2-ol to butanone.[82] This approach was inspired by $[RuCpCl(PPh_3)_2]$, a very efficient catalyst for the isomerization of allylic alcohols into carbonyl compounds.[83-85] Most of the complexes showed high activity for the isomerization reaction (Scheme 1.14a), however, in the presence of a conjugated diene no isomerization was observed at all. Some of these complexes, in the presence of a conjugated diene (in this case isoprene) showed an unexpected, but interesting activity: formation of diallyl ethers (Scheme 1.14b).

After the first finding of this catalytic ether forming reaction of 3-buten-2-ol, allyl alcohol was used as the substrate. The turnover frequency (TOF) was found to be somewhat lower than observed for ether formation of 3-buten-2-ol, but selectivity towards ether formation appeared very high. Several ruthenium complexes were investigated for their activity in ether formation (Figure 1.3), of which catalyst **D** had the highest activity in the formation of diallyl ether (DAE) with a TOF of 615 h^{-1}. Addition of isoprene slowed down the reaction. Extension of the carbon-chain length between the phosphorous donors in the bidentate ligands resulted in a decrease of the catalytic activity.

Since catalyst **D** gave the highest activity in the formation of DAE, this catalyst was also used in the cross-allylation of other nucleophiles. The conditions necessary for cross coupling however turned out to be more severe than for the homo coupling. Addition of *p*-cresol to the reaction mixture gave, next to DAE, a considerable amount of allyl (*p*-methylphenyl) ether,



Scheme 1.14. Ruthenium-catalyzed a) isomerization and b) allylation of allyl alcohols.

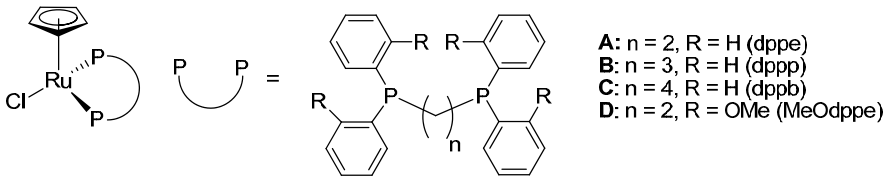
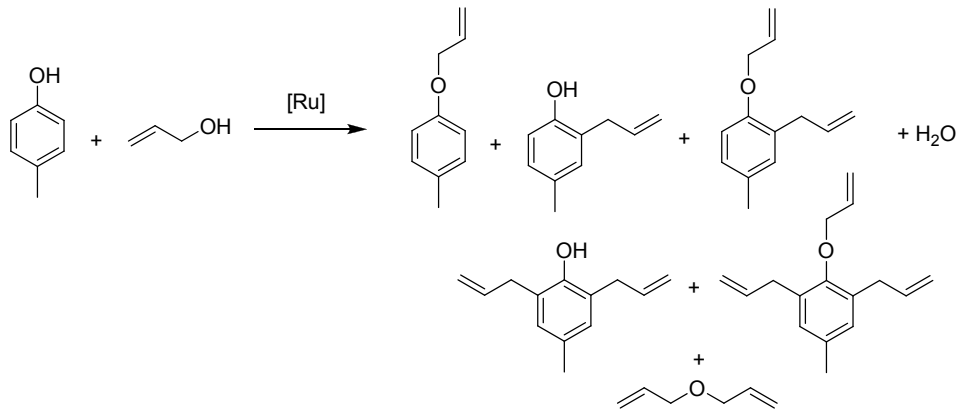


Figure 1.3. Structures of ruthenium complexes showing activity in the catalytic allyl ether formation.[82]

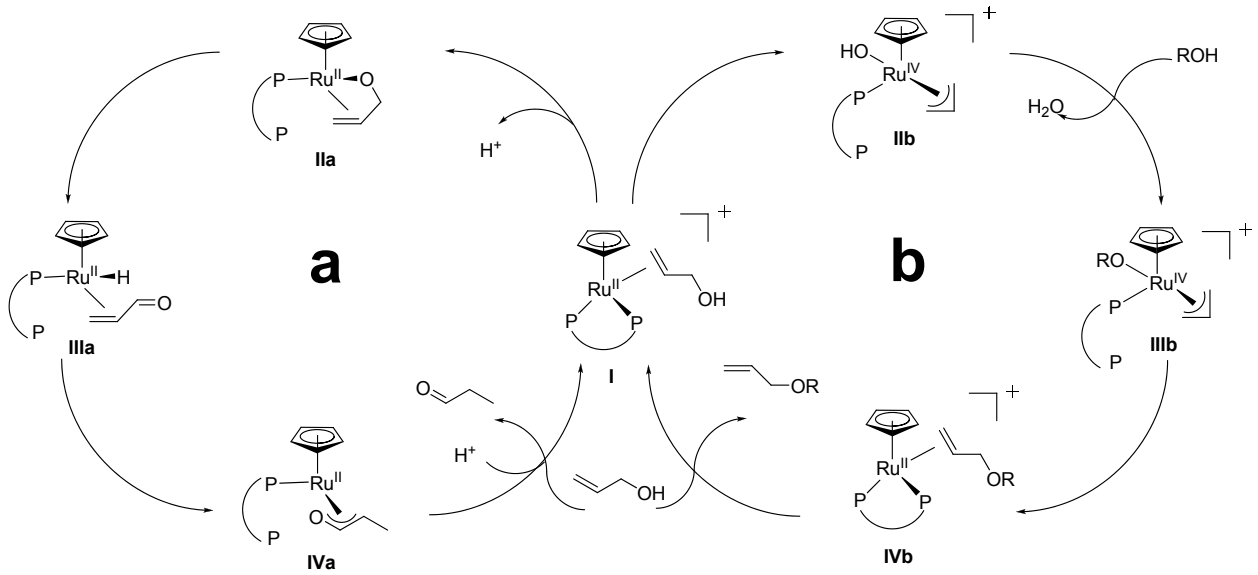
making it the first $[RuCp(PP)]^+$ complex that catalyzes O-allylation in the absence of stoichiometric amounts of base. The catalyst is also quite active and only low concentrations of catalyst are needed. However, the formed allyl phenyl ether undergoes further reactions, yielding a mixture of several ring allylated cresols and ethers (Scheme 1.15), which have been proposed to be formed via a Claisen rearrangement. The proposed mechanisms are shown for both the isomerization of allyl alcohol in Scheme 1.16a, as well as the catalytic O-allylation in Scheme 1.16b.

After coordination of allyl alcohol onto the cationic Ru(II) complex via the olefin moiety, two possible reactions can take place. When the alcohol deprotonates and a phosphine dissociates the formed allyl alkoxide can coordinate in a bidentate fashion, forming species **IIa.** Subsequent β-hydrogen abstraction (**IIIa**), followed by a reinsertion of the hydride (**IVa**) and protonation yields the aldehyde. The allylation reaction occurs when the Ru-bound allyl alcohol undergoes an oxidative addition (**IIb**). The formed hydroxide anion deprotonates the alcohol, thereby forming water and an alkoxide anion (**IIIb**). After reductive elimination, an allyl ether is formed (**IVb**) and after replacement of this ether with a molecule of allyl alcohol, the catalytic cycle is completed and **I** is obtained.

The research discussed in this section was used as a starting point for the research described in his thesis.



Scheme 1.15. Product formed in catalytic allylation of p-cresol with allyl alcohol in the presence of $[RuCp(PP)]^+$.



Scheme 1.16. Proposed mechanism of the catalytic a) isomerization and b) allylation of allyl alcohol by a ruthenium complex.[82]

1.3 Phosphine ligands

1.3.1 General

The catalysts tested by van der Drift *et al.* were $[RuCp(PP)]^+$ complexes, both with monodentate and bidentate phosphine ligand. Phosphines are some of the most common ligands associated with transition metal complexes and homogeneous catalysis. An advantage of using phosphine ligands is that their properties can be changed systematically by changing the functional groups attached to phosphorous. A tailor-made ligand can be designed to provide in the needs of the transition metal catalyst. Furthermore, specific geometries of ligands around the metal centre can influence the rate and selectivity of a reaction. A reaction pathway can be altered by ligands that either stabilize the initial geometry, the transition state or the final geometry of a complex. When the formation of an intermediate that follows after the rate-determining step is promoted by the type of ligands used, activity will be increased. Selectivity towards a single product is promoted by favoring formation of one specific intermediate, while inhibiting formation of an intermediate towards another product in the selectivity-determining step.

1.3.2 Monodentate phosphine ligands

The properties of phosphine ligands bearing different R substituents originate from two type of interactions, being electronic or steric interactions. These two interactions cannot always be

Table 1.1. Electronic and steric properties of phosphine ligands.

Ligand	$\Delta\nu$	θ
P(*t*-Bu)$_3$	0	182
PCy$_3$	0.3	170
P(*o*-MeOPh)$_3$	2.7	-
PMe$_3$	7.8	118
P(*p*-MeOPh)$_3$	10.2	-
P(*o*-tol)$_3$	10.5	145-194
PPh$_3$	12.9	145
PPh$_2$H	16.9	128
P(OEt)$_3$	20.4	109
PH$_3$	24.9	87
P(OPh)$_3$	29.1	128
PF$_3$	54.6	104

clearly separated and are sometimes related. However, a useful classification was made by Tolman using the parameters $\Delta\nu$ and θ,[86] now (not surprisingly) known as the Tolman parameters.

The electronic parameter $\Delta\nu$ of a phosphine ligand is a quantification of its electronic properties, caused by donation of electron density along chemical bonds. Table 1.1 contains the $\Delta\nu$ values of a selection of phosphine ligands.[87] Phosphines with a low $\Delta\nu$-value are considered to have high σ-donating and poor π-accepting character, while phosphines with a high $\Delta\nu$-value are considered to have poor σ-donating and high π-accepting character. The nature of the substituents on phosphorous determines $\Delta\nu$ and in general, phosphines with electron-donating groups, like alkyl or *o*-anisyl (*o*-MeOPh), have a low $\Delta\nu$-value, while phosphines with electron-withdrawing groups like alkoxy or phenoxyl, have a high $\Delta\nu$-value . Such electronic characters are crucial for the (de)stabilization of complexes containing the corresponding phosphine ligands.

The steric properties of a phosphine ligand are quantified by the ligand cone angle θ. These cone angles are obtained from a space-filling model of the Ni(PR$_3$) group.[86] The θ-value of some representative ligands are given in Table 1.1.

1.3.3 Bidentate ligands

Chelating bidentate ligands can enforce a specific geometry to the complex, because of the limitations in P-M-P angles set by the bridging group between the two phosphorous donors.

The natural bite angle β is defined as the preferred chelation angle determined by the ligand. This definition was introduced by Casey and Whiteker and based on molecular mechanics calculations.[88] The natural bite angle is mainly governed by constraints due to the ligand

backbone and steric repulsion between substituents on the phosphorous donor and substituents on the ligand backbone. In an actual complex, however, the P-M-P angle is always a compromise between the natural bite of the ligand and the coordination angle preferred by the metal(ion). Dierkes *et al.* collected P-M-P fragments in X-ray-determined crystal structures from the Cambridge Structural Database (version October 1997) and reported the average angle for a selection of ligands.[89] A selection was made from the table published by Dierkes *et al.*[89] and the data are shown in Table 1.2.

Both the effect of increasing the carbon bridge length and changing the substitution of phosphorous on the coordination angle are clearly observed (Table 1.2). Going from entry 1 to entry 2 to entry 4, the coordination angle clearly increases when the bridge between the phosphorous atoms is increased from a C_1 to a C_2 and C_3, respectively. When even larger bridge structures are used (entries 7-11) the angles increase gradually. Besides the bridging group, also the other substituents on phosphorous have an effect on the preferred coordination angle. When the phenyl groups from dppe (entry 2) are replaced with the highly sterically demanding *tert*-butyl group in dtbpe (entry 3), the coordination angle increases due to the increase in steric repulsion of these groups. A same trend is observed for the series dppp (entry 4), dmpp (entry 5) and dtbpp (entry 6).

Although monodentate phosphine ligands do not have an actual bite angle, a P-M-P angle is present when two phosphines are coordinated onto a metal. When PPh_3-M-PPh_3 fragments are collected in X-ray-determined crystal structures from the Cambridge Structural Database (version October 2008)[90] and the P-M-P angles are plotted against the number of hits for this specific angle, a graph as shown in Figure 1.4 is the result.

From this figure, two distinct peaks are observed, one centered around 100° and one centered around 176°. The peak around 100° correlates with complexes in which the

Table 1.2. Average coordination angles for cis-coordinated bidentate phosphine ligands.

Entry	Ligand[a]	P-M-P angle (σ)° [b]
1	dppm	72 (2)
2	dppe	83 (4)
3	dtbpe	90 (2)
4	dppp	92 (4)
5	dmpp	91 (2)
6	dtbpp	100 (2)
7	dppb	97 (3)
8	dppf	99 (3)
9	binap	93 (2)
10	dpppe	101
11	xantphos	105

[a] abbreviations are explained in list of abbreviations.
[b] standard deviations (σ) indicated in parentheses.

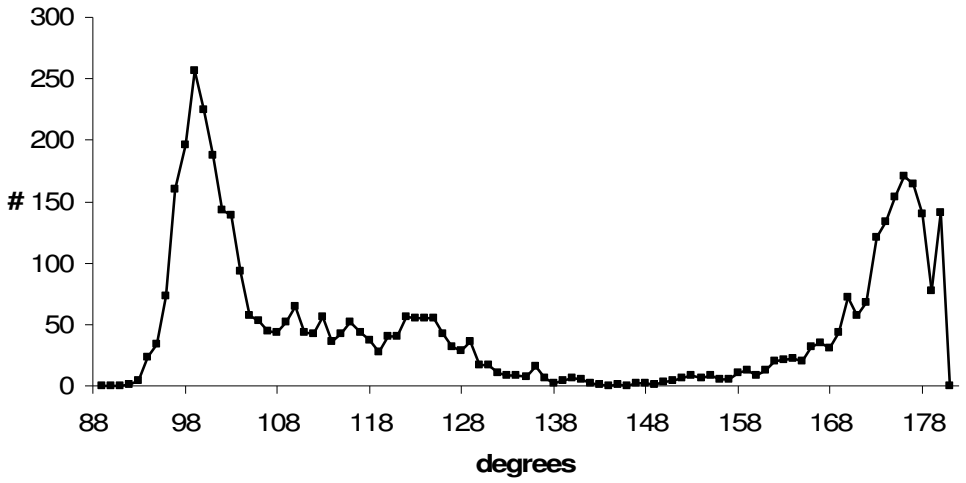


Figure 1.4. Number of (PP)M fragments (#) with P = PPh_3 found in a CSD search**.**

triphenylphosphine ligands are coordinated in a cis-orientation. When this angle is compared with the angles of bidentate phosphine ligands, the P-M-P angle (P = PPh_3) is relatively large and competes with the bidentate ligands with large bite angles. The peak around 176° correlates with the many complexes on which the triphenylphosphine ligands are trans coordinated. So although not a bidentate ligand, two triphenylphosphine clearly have a favored P-M-P angle.

Due to the restrictions induced by the ligand on the coordination angle, certain geometries in the complex will be favored over others. For example, in a trigonal bipyramidal complex, ligands with a bite angle of 120° will enforce a di-equatorial coordination, but diphosphine ligands with a bite angle of 90° will enforce an axial-equatorial coordination. Besides the geometry of the complex, also the coordination number and stereochemistry can be influenced by bidentate ligands. Depending on the length of the chain between the two donor atoms, the chelate will coordinate either with *cis* or *trans* configuration, thereby forcing the other ligands in the same configuration.

The bite angle in a metal complex is tuned, within the limits sets by the flexibility of the ligand backbone, to the optimal angle for orbital overlap with the metal. This angle is roughly 90° for cis-coordination in square-planar or octahedral complexes, 120° for bis-equatorial coordination in trigonal-bipyrimidal complexes and 180°: for trans-coordination in square-planar complexes.

The effects of the P-M-P angle on catalytic reactions have both steric and electronic origin. The steric effects are caused by ligand-ligand or ligand-substrate steric interactions. The P-M-P angle determines the reaction space for substrates. The available reaction space imposed by

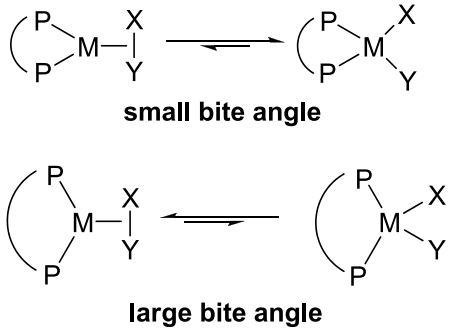


Figure 1.5. a) steric influence of P-M-P angle on reaction space α and b) influence of reaction space on oxidative addition and reductive elimination.

the sterics of the ligand, causes that certain intermediates and transition states in the catalytic cycle can be stabilized or destabilized. In Figure 1.5 an example is given where for large P-M-P angles, reductive elimination is promoted, while oxidative addition is suppressed. For small P-M-P angles the opposite is the case.

Apart from the steric effect of the P-M-P angle, also electronic effects induce by this angle play an important role in the catalysis. Due to the change of the P-M-P angle, the overlap of the orbitals of the metal and the phosphorous donor atoms changes. This applies for both σ-donation from the ligand to the metal as well as π-backbonding from the metal to the phosphine ligand. As a results of the change in orbitals overlap, the electron density on the metal center also changes, which influences especially redox reactions, but also the coordination behavior of the complex towards certain substrates.

Effects of bite angles on catalytic reactions, such as hydroformylation, CO/ethene polymerization and allylations have been widely studied and several review articles have been published.[91-93]

1.4 Aim and contents of this Thesis

The finding of the first Ru catalysts that catalyze the O-allylation of a phenol with allyl alcohol in the absence of stoichiometric additives by van der Drift forms the starting point for the present research. Unfortunately, beside the desired O-allylated product undesired C-allylated products are also formed in a large amount. Thus far, no catalytic system has been reported that can indeed convert a phenol and allyl alcohol with high selectivity into an allyl phenyl ether and water, without the addition of stoichiometric (base) additives.

The long-term goal of the present research is the development of highly active and selective catalysts for the O-allylation of phenols, and ultimately, in particular di-phenols, with an environmentally acceptable allyl source, such as allyl alcohol.

The mechanism by which the respective O- and C-allylated products are formed is still largely unknown. Of course, for the development of selective O-allylation catalysts it is highly desirable to obtain mechanistic molecular insight into the catalysis underlying the allylation reactions. It is expected that such a molecular understanding will allow the design of catalyst structures for optimal performance. In particular, the molecular connection between the structural properties of catalyst complexes and their catalytic performance needs to be uncovered. The research described in subsequent chapters of this thesis is aimed at gaining this knowledge.

In **Chapter 2**, the synthesis of a series of cationic $[RuCp(PP)]^+$ complexes is reported and their subsequent activity as catalysts for allylation of phenols with allyl alcohol. Several novel key aspects of this type of reaction are found and a general mechanism is proposed.

Chapter 3 builds on upon the results of chapter 2 and a series of selective catalyst for O-allylation of phenol with allyl alcohol is designed. The bidentate phosphine ligand is chosen in such a way that selectivity of the reaction can be controlled.

Chapter 4 deals with a surprising finding, which has led to a catalyst that is not only very selective, but also incredibly active. Very high turnover numbers are achieved and a explanation is given for the combined high activity, selectivity and stability of the catalytic system.

The range of substrates is expanded in **Chapter 5** by investigating the reactivity of aliphatic alcohols with allyl alcohol with Ru-catalyst found to be active for allylations in the previous chapters. Initially, allyl alcohol is used as the allylating agent, but in the second part of the chapter also substituted allyl alcohols are reacted.

Chapter 6 deals with the immobilization of the Ru-catalysts found to be active for allylation reaction. Two different approaches are used, being immobilization via a electrostatic interaction and immobilization via an coordination bond. After immobilization, the catalysts are tested for activity and stability in allylation reactions.

In **Chapter 7** a detailed mechanistic discussion is held and supported by DFT calculations. The proposed Ru intermediates present in the catalytic cycle are compared by means of energy differences, especially those playing a important role for activity and selectivity of the catalyst in allylations.

Besides ruthenium, also palladium complexes are used as catalysts for allylations of phenols and the results are shown and discussed in **Chapter 8**. Complexes with different phosphine ligands are screened for activity and selectivity in the allylation of phenols with allyl alcohol. Besides phenols, other substrates are also allylated. Similarities and dis-similarities between Pd and Ru complexes as allylation catalysts are discussed and placed in a mechanistic context.

In **Chapter 9**, bisphenol A is investigated for its reactivity in catalytic O-allylation. A selection of different selective O-allylation catalysts is tested with the goal to obtain the diallylther of BPA in high yield with low amounts of C-allylated products.

Chapter 10 contains the summary and conclusions, followed by future prospects.

Parts of this thesis have been published,[94-96] filed as patents[97-99] or submitted for publication.[100,101]

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2

Cationic ruthenium-Cp-diphosphine complexes as catalysts for the allylation of phenols with allyl alcohol

Abstract
A new catalytic method has been investigated to obtain either O- or C-allylated phenolic products using allyl alcohol or diallyl ether as the allyl donor. With the use of new cationic ruthenium(II) complexes as catalyst, both reactions can be performed with good selectivity. Active cationic Ru(II) complexes, having cyclopentadienyl and bidentate phosphine ligands are generated from the corresponding Ru(II) chloride complexes with a silver salt. The structures of three novel (diphosphine)Ru(II)CpCl catalyst precursor complexes are reported. It appears that the structure of the bidentate ligand has a major influence on catalytic activity as well as chemoselectivity. In addition, a strong cocatalytic effect of small amounts of acid is revealed. Model experiments are described that have been used to build a reaction network that explains the origin and evolution in time of both O-allylated and C-allylated phenolic products. Some mechanistic implications of the observed structure vs. performance relation of the $[RuCp(diphosphine)]^+$ complexes and the cocatalytic role of added protons are discussed.

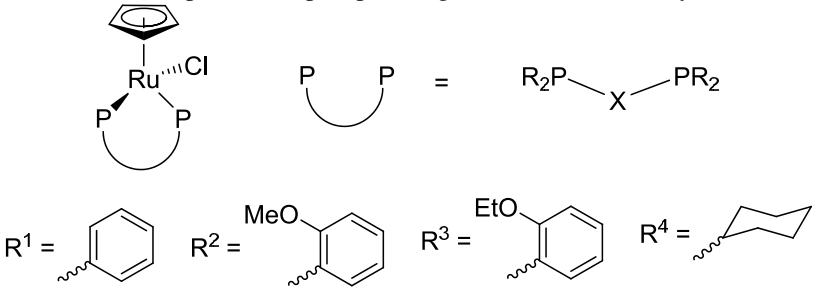
This Chapter is based on: J.A. van Rijn, M. Lutz, L.S. von Chrzanowski, A.L. Spek, E. Bouwman, E. Drent, Adv. Synth. Cat. 2009, 351, 1637 – 1647.

2.1 Introduction

For catalytic allylation reactions, allyl substrates with good leaving groups like carboxylate and halide have been employed in combination with ruthenium and palladium catalysts. In these reactions generally a stoichiometric amount of base is added to induce O-allylation, thereby producing inorganic salts as sideproducts.[1-3] In the context of the development of an environmentally benign catalytic route to epoxy resins, the O-allylation of phenols is desired.[4] Allyl phenyl ethers can be epoxidized to obtain glycidyl ethers, which are currently produced on a multi-hundred kilotonne/year scale in the epoxy resin industry via the conventional epichlorohydrin route with the coproduction of stoichiometric amounts of chloride salt waste. From an environmental and atom-efficiency point of view it would be attractive to use allyl alcohol as the allyl donor, as only water is coproduced. However, the Pd systems for phenol allylation all use stoichiometric amounts of base [Ti(O*i*Pr)$_4$] to induce O-allylation,[5] or Lewis acid (BEt_3) to promote C-allylation.[6] With such Pd systems, electron-rich phenols such as 3,5-dimethoxyphenol and 1-naphthol were selectively C-allylated with allyl alcohol into 4-allyl-3,5-dimethoxyphenol and 2-allyl-1-naphthol, respectively, of which the latter does not require the use of a stoichiometric amount of base.[5,7] In one example, C-allylation of phenols in an aqueous environment is induced by adding large amounts of base to the system.[8] The yields in this system are very low. Using a Pd/Ti(*Oi*Pr)$_4$ system, also aniline can be allylated with allyl alcohol.[9] Although O-allylation of aliphatic alcohols was previously reported,[10] phenols appeared to be much less reactive.

Only a few examples report catalytic allylation of phenols using allyl alcohol without the need of stoichiometric additives, which are based on ruthenium catalysts.[11,12] Pregosin and co-workers have described a system that is able to C-allylate phenols.[11] Finally, a CpRu(diphosphine) system was reported earlier with which both O-and C-allylated products were formed. It was proposed that under the applied reaction conditions a thermal uncatalyzed Claisen rearrangement of O-allylated product occurred resulting in a mixture of O- and C-allylated products.[12] In the present chapter, the influence of the diphosphine ligand (Table 2.1)

Table 2.1. The ruthenium complexes and phosphine ligands used in this study with their abbreviations.



X	R	abbreviation
methylene	R^1	dppm
1,2-ethylene	R^1	dppe
1,3-propylene	R^1	dppp
1,4-butylene	R^1	dppb
methylene	R^2	*o*-MeOdppm
1,2-ethylene	R^2	*o*-MeOdppe
1,3-propylene	R^2	*o*-MeOdppp
1,2-ethylene	R^3	*o*-EtOdppe
1,2-ethylene	R^4	dcpe

in cationic Ru(II) Cp complexes on their performance in the catalytic allylation of 4-*tert*-butylphenol with allyl alcohol is explored. It will be shown that chemoselectivity of cationic RuCp(diphosphine) complexes, in situ produced from the corresponding neutral Ru chloride precursor by addition of AgOTs (in the absence of AgOTs hardly any activity is observed), is decisively controlled by the diphosphine ligand. In particular, it will be shown that the steric properties of the diphosphine ligand are also critically important for the Ru-catalyzed conversion of the O-allylated product into thermodynamically more favourable C-allylated products. In addition, evidence will be given of a strong cocatalytic effect of small amounts of added acid, not only on the rate, but surprisingly also on the course of the allylation reactions.

2.2 Results and discussion

2.2.1 Synthesis

The new ruthenium complexes were successfully synthesized by displacement of the monodentate triphenylphosphine in [RuCpCl(PPh_3)$_2$] with bidentate phosphine ligands, with complex yields in the range of 80–85%. Reaction temperatures below 100 °C were used in the synthesis of the complexes with the ligands bearing *ortho*-substituents on the phenyl rings. When higher temperatures were used, methyl chloride or ethyl chloride was eliminated from the complex, resulting in a chelating phenolate group.[13] For the unsubstituted ligands, a slight excess of ligand was used to ensure complete conversion of the starting material. The excess of ligand and the displaced triphenylphosphine could be easily separated from the product by

flushing the reaction mixture over a small silica gel column with toluene. The orange product band is immobile when toluene is used as the eluents and it can be eluted with ethyl acetate. Exactly one equivalent of the ortho-substituted ligands compared to ruthenium was used, as it proved to be difficult to remove excess of ligand from the mixture, either by flash silica gel chromatography or crystallization. All complexes have been characterized with ^{1}H- and ^{31}P NMR spectroscopy and elemental analysis.

2.2.2 Crystal Structures

The molecular structures of [RuCpCl(*o*-EtOdppe)], [RuCpCl(*o*-MeOdppm)] and [RuCpCl(*o*-MeOdppp)] are shown in Figure 2.1. Selected bond distances and angles are listed in Table 2.2. The binding of the ruthenium ion to the bidentate phosphine ligand is slightly asymmetrical in [RuCpCl(*o*-EtOdppe)] and [RuCpCl(*o*-MeOdppp)], while in [RuCpCl(*o*-MeOdppm)] the Ru–P distances are equal. The distances of the ruthenium centre to the cyclopentadienyl group and the chloride anion are similar for all three compounds and are comparable to those of related ruthenium complexes.[14-17] The distance of the oxygen atoms O(17) and O(47) to Ru is too large [3.7932(17)–4.2351(14) Å] for all of the structures to be considered as an interaction, however, they are close enough to sterically block the metal centre. The two other oxygen atoms, O(27) and O(37), are relatively far away from the ruthenium atom [5.1764(15)–5.3428(13) Å]. The P···O distances are smaller than the sum of the van-der-Waals radii. The bite angles of the phosphine ligands very clearly reflect the

Table 2.2. Selected bond lengths and angles for the complexes [RuCpCl(*o*-EtOdppe)] (**a**), [RuCpCl(*o*-MeOdppm)] (**b**) and [RuCpCl(*o*-MeOdppp)] (**c**).

	(**a**)	(**b**)	(**c**)
Bond distances (Å)			
Ru(1)-Cl(2)	2.4456(13)	2.4363(5)	2.4653(4)
Ru(1)-P(3)	2.2711(16)	2.2947(4)	2.2967(4)
Ru(1)-P(7)	2.2958(14)	2.2926(4)	2.2644(4)
Ru(1)-Cp	1.8395(5)	1.8386(2)	1.8449(1)
Ru(1)...O(17)	4.094(4)	3.7975(14)	3.8416(13)
Ru(1)...O(47)	3.927(4)	3.7932(17)	5.2343(15)
Ru(1)...O(27)	5.260(4)	5.2606(16)	5.3428(13)
Ru(1)...O(37)	5.298(3)	5.1764(15)	4.2351(14)
P(3)...O(17)	2.967(5)	2.9073(13)	2.9365(13)
O(17)...O(27)	3.443(6)	4.649(2)	3.7891(19)
O(37)...O(47)	4.174(5)	4.760(2)	3.176(2)
Angles (°)			
P(3)-Ru(1)-P(7)	83.43(6)	72.145(16)	92.591(15)
P(3)-Ru(1)-Cl(2)	86.10(5)	90.147(16)	85.646(15)
P(7)-Ru(1)-Cl(2)	91.55(5)	90.131(16)	86.753(15)

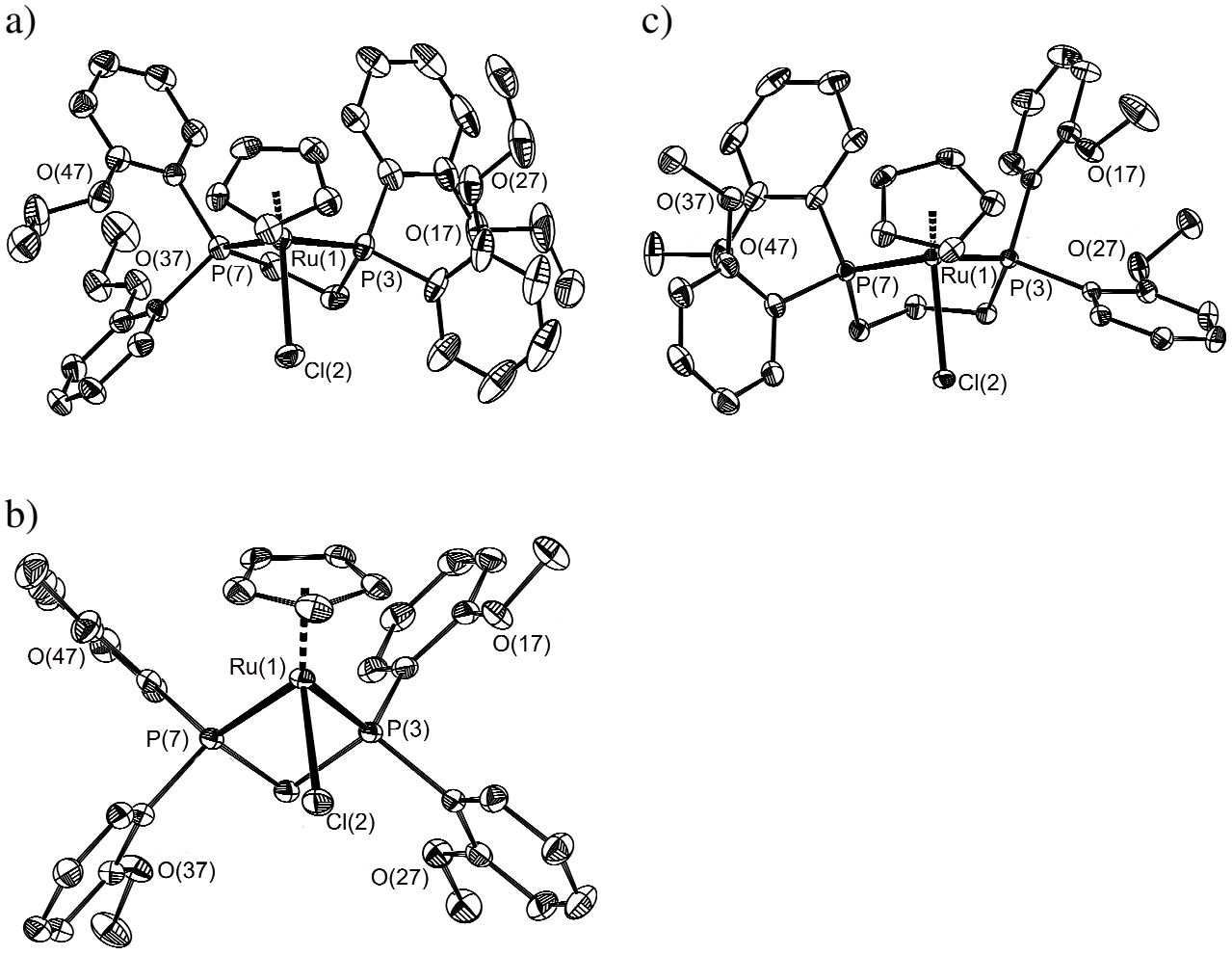
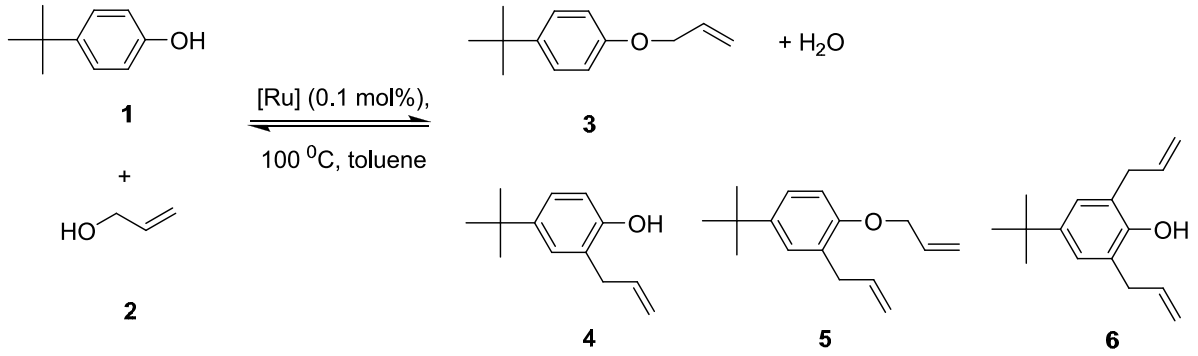


Figure 2.1. Displacement ellipsoid plots of a) [RuCpCl(*o*-EtOdppe)], b) [RuCpCl(*o*-MeOdppm)] and c) [RuCpCl(*o*-MeOdppp)] with the adopted atom labelling. Displacement ellipsoids are drawn at the 50% probability level. Hydrogen atoms are omitted for clarity. The (disordered) solvent molecules in the structure of [RuCpCl(*o*-MeOdppm)] are not shown.

increase of the carbon chain bridge in these three complexes, going from 72 via 83 to 93° for the methylene, ethylene and propylene bridges, respectively.

2.2.3 Catalytic Allylation

The complexes were tested in the reaction shown in Scheme 2.1. A low catalyst loading of 0.1 mol% was used at a temperature of 100 °C. Apart from the O-allylated product **3**, the C-allylated products **4–6** were observed (Scheme 2.1). The products were isolated and characterized by NMR and GC/MS. The evolution of phenol-derived products in a typical experiment, using [RuCp(*o*-EtOdppe)](OTs) as catalyst precursor, is shown in Figure 2.2. From this it can be seen that in the first 30 min the formation of O-allylated product **3** is very rapid, however, after about one hour the amount of **3** starts to decrease in time. A similar (but less pronounced) concentration profile is observed for **5**.



Scheme 2.1. Model reaction of 4-*tert*-butylphenol **1** and allyl alcohol **2** catalyzed by ruthenium complexes showing the multiple of phenol-derived products **3**-**6**.

The concentration of C-allylphenols **4** and **6** steadily increases in time. After long reaction times (>12 h) almost only the C-allylated products **4** and **6** are observed. These concentration profiles thus indicate that the growth of **4** and **6** occurs at the cost of respectively **3** and **5** by a consecutive reaction. Apparently, **4** and **6** are the thermodynamic end products.[18]

After the first hour, the conversion of phenol hardly changes, however, the product composition changes in a major way. It thus appeared that the selectivity of the phenol allylation reaction to the respective products (**3**–**6**) is reaction time-dependent, but the product composition also strongly depends on the structure of the Ru catalyst used. The results for a series of Ru phosphine complexes are listed in Table 2.3; some clear trends can be observed.

Looking at the phosphines with unsubstituted phenyl groups, there is an optimum in activity with a 1,2-ethylene bridging group in the ligand. [RuCp(dppm)] (OTs) (entry 1) is more than an order of magnitude less active (k = 0.06 h^{-1}) than [RuCp(dppe)](OTs) (entry 2, k = 1.19 h^{-1}),[19] while the high selectivity for the C-allylated product 4 with the small bite-angle (~72°) dppm ligand is remarkable. This suggests that the formation of the C-allylated product requires a relatively large free coordination space at Ru for this reaction to occur. Increasing

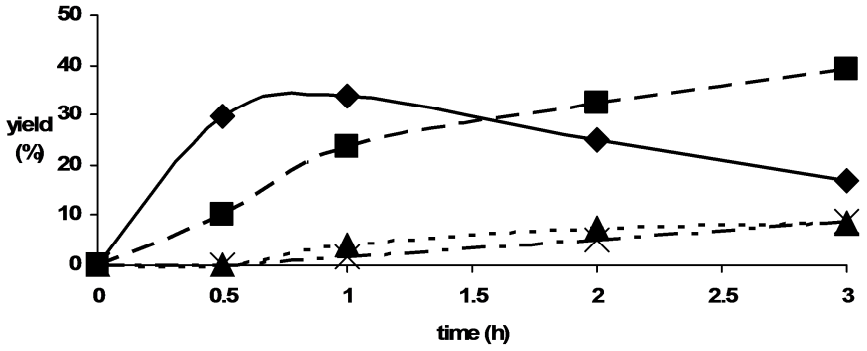


Figure 2.2. Formation of phenol-derived products in the reaction of 4-te*rt*-butylphenol with allyl alcohol in time in a typical experiment; (♦) **3** (■) **4** (▲) **5** (×) **6**. Reaction conditions: ratio 4-*tert*-butylphenol/allyl alcohol/[RuCpCl(*o*-EtOdppe)]/AgOTs = 1000/1000/1/2. toluene, 100 °C. 5 mmol of phenol was used.

Table 2.3. Reaction of 4-*tert*-butylphenol (**1**) with allyl alcohol (**2**) catalyzed by different [RuCp(PP)]$^+$complexes. [a]

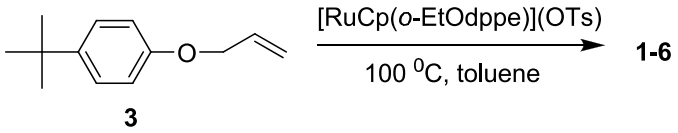
entry	RuCp(PP) PP =	conversion of **1** (%)			k^c (h^{-1})	selectivity (%)							
						3	**4**	**3**	**4**	**3**	**4**	**5**	**6**
		0.5 h	1 h	3h		0.5 h [e]		1 h [e]		3 h			
1	dppm	3	7	21	0.06	8	92	3	89	2	93	2	3
2	dppe	45	56	72	1.19	47	47	38	53	4	56	12	28
3	dppp	24	42	53	0.55	80	20	70	30	44	47	6	3
4	dppb[b]	0	0	0	0	-	-	-	-	-	-	-	-
5	PPh_3[b]	0	0	0	0	-	-	-	-	-	-	-	
6	dcpe	4	10	34	0.08	81	19	76	18	76	22	1	1
7	*o*-MeOdppm	6	15	39	0.12	13	84	7	90	4	90	0	6
8	*o*-MeOdppe	44	53	60	1.15	58	42	39	51	12	74	5	9
9	*o*-EtOdppe	40	63	73	1.02	67	33	53	38	23	54	11	12
10	*o*-MeOdppp	0	7	21	0.07	-	-	99	1	87	13	0	0
11	*o*-EtOdppe[d]	80	84	87	3.22	92	8	81	13	53	20	18	9

[a] Reaction conditions: ratio 4-*tert*-butylphenol/allyl alcohol/[Ru]/AgOTs = 1000/1000/1/2, toluene, 100 °C.
[b] active in the isomerization of allyl alcohol into propanal.
[c] after 0.5 h
[d] with diallyl ether instead of allyl alcohol.
[e] in cases **3** and **4** do not add up to 100%, the remainder is product **5** and **6**

the bridge length from 1,2-ethylene to 1,3-propylene (bite angles respectively ~83° and 92°) leads to a decrease in activity (entry 3, k=0.55 h^{-1}), but with a significant increase in selectivity for O-allylation. In contrast, with a 1,4-butylene bridge (bite angle 94°, entry 4), all activity for allylation is lost. Instead, the complex appears active in the isomerization of allyl alcohol into propanal. The complex with two monodentate phosphine ligands (entry 5) is a very active catalyst in this isomerization reaction, in agreement with a prior report,[20] and shows no activity at all towards allylation. When the phenyl groups of the thus far most active dppe complex are replaced by cyclohexyl groups, the initial activity drops considerably (from k=1.19 h^{-1} to k=0.08 h^{-1}), but the selectivity for O-allylation increases significantly from 40% to 76% (entry 6).

When the phenyl groups of the phosphines are substituted with ortho-methoxy groups, a similar reactivity pattern is observed. [RuCp(*o*-MeOdppm)](OTs) (entry 7) is, like its unsubstituted analogue, very selective in the formation of C-allylated product 4. There is again an optimum in activity with an ethylene bridging group (entries 8 and 9). The complexes with a methylene or 1,2-ethylene bridge in the ligand (entry 7–9) show a similar or higher activity compared to their unsubstituted analogues (entry 1 and 2). The [RuCp(*o*-MeOdppp)](OTs) complex, however (entry 10), unexpectedly is considerably less active than its unsubstituted analogue, but it is highly selective for the formation of **3**. Having a very similar activity as the catalyst based on dppm (entry 1), the contrast in chemoselectivity is remarkable. Finally, not only allyl alcohol can be used as allylating agent, but also diallyl ether (entry 11). In all reactions diallyl ether is formed initially from allylation of allyl alcohol itself, forming water in the process. The diallyl ether further reacts with **1** to form **3**–**6**. It

Table 2.4. Reaction of **3** in the presence of [RuCp(*o*-EtOdppe)](OTs) and different additives.[a]



3

entry	additives	conversion of **3** (%)	selectivity (%) **1**	**4**	**5**	**6**
1	-	0	0	0	0	0
2	H_2O[b]	99	20	55	3	22
3	*p*-cresol[c]	92	40	54	2	4
4	HOTs [d]	86	33	40	3	24
5	camphor sulfonic acid	49	28	44	21	7

[a] Reaction conditions**:** ratio **3/**[RuCpCl(*o*-EtOdppe)]/AgOTs = 1000/1/2, 100 °C, 2 h. If added, additives in ratio **3**/H_2O/cresol/HX = 1000/1000/1000/2
[b] after 18 h
[c] yields are total of both 4-*tert*-butylphenol and *p*-cresol derived products
[d] HOTs = *p*-toluenesulfonic acid

appears that the activity and selectivity of the catalyst are highly enhanced if diallyl ether is used as the allyl source, possibly because less water is formed.

2.2.4 Reactivity of Allyl Ethers

An intriguing aspect of the evolution of products in the course of the reaction shown in Figure 2.2, is the question by which mechanism the concentration of initially formed O-allylated products **3** (and **5**) decrease at longer reaction times, while in parallel C-allylated products **4** (and **6**) steadily increase. As it is observed that diallyl ether can also be used as allylating agent as a substitute for allyl alcohol, it was suspected that the product ether **3** itself would also show reactivity towards the catalyst. Thus, phenyl allyl ether **3** was exposed to several conditions and additives to investigate its reactivity both under thermal conditions in the absence of the ruthenium catalyst as well as under prevailing catalytic conditions. The results are given in Table 2.4. When **3** is exposed to allylation reaction conditions with any of the reagents present in a typical reaction mixture, but in the absence of a catalyst, no reaction is observed, thus excluding the possibility of a thermal Claisen-type rearrangement. Adding only [RuCp(*o*-EtOdppe)](OTs) to **3** in toluene also gives no conversion (entry 1). In contrast, when both the Ru catalyst and a stoichiometric quantity of water with respect to **3** are present, compound **3** is fully converted in 18 h to give 4-*tert*-butylphenol, allyl alcohol, and C-allylated products **4–6** (entry 2). Under these conditions conversion of **3** takes place only after an induction period of several hours. However, when a stoichiometric amount of *p*-cresol is added, a conversion of **3** of 92% is observed after only two hours residence time; not only products **4–6**, but also the analogous *p*-cresol-derived allylation products are formed as well

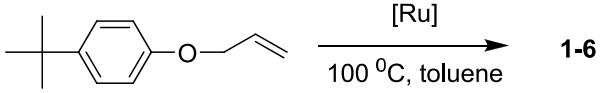
as 4-*tert*-butylphenol by transetherification. At this stage it is hypothesized that the added *p*-cresol – or likewise the 4-*tert*-butylphenol generated by the hydrolysis of **3**, – would function as an acidic cocatalyst, and have a devastating effect on the selectivity for O-allylation to give C-allylation instead. Therefore, the activated Ru catalyst is supplemented with a catalytic amount of hydrated *p*-toluenesulfonic acid (HOTs·xH_2O) and observed that **3** was now reacted to form **1** and products **4–6** with a conversion of 86% in only two hours. When this reaction is performed with a catalytic amount of camphorsulfonic acid under strictly anhydrous conditions (entry 5), a conversion of **3** of 49% after two hours is achieved to give again a mixture of products **1–6.** It should be noted that the combined amount of **5** and **6** is equal to the amount of **1**, since the total number of allyl moieties remains constant. In summary, in the presence of Ru catalyst and water, hydrolysis of **3** to phenol **1** and allyl alcohol **2** can take place, showing that O-allylation is a reversible reaction that is thermodynamically limited. The conversion to O-allylated product in a batch allylation process will thus be limited by the concentration of water in the reaction medium at reaction temperature. However, the utilization of an apolar solvent such as toluene allows the reaction to proceed beyond its thermodynamic equilibrium as the solubility of water in the reaction medium is low and water will form a separate phase. In order to prevent the reversed reaction of **3** in a batch process, an experiment was executed in which water was removed from the system by means of a Dean–Stark trap. A conversion of 85% with a selectivity towards O-allylated product **3** of 80% was observed after 30 min. An initial catalyst TOF of about 1700 h^{-1} was thus achieved. For the reaction of the phenol 1 and allyl alcohol 2 with [RuCp(*o*-EtOdppe)](OTs) as catalyst, it was found that adding catalytic amounts of a Brønsted acid affects both the selectivity and the rate of the reaction. When a catalytic amount (2 equivalents on Ru-complex) of strong acid in the form of HOTs is added the rate of the reaction increases in a dramatic way to an initial turnover frequency of 6200 h^{-1} in the first 5 min, while for this catalytic system the selectivity completely shifts towards C-allylation. For the acidic system in the absence of Ru complex, no activity is observed, excluding the possibility of an acid-catalyzed reaction.

Table 2.5. Reaction of 4-*tert*-butylphenol (**1**) with allyl alcohol (**2**) catalyzed by different [RuCp(PP)]$^+$complexes in the presence of added HOTs.[a]

entry	RuCp(PP) PP =	conversion of **1** (%)			k (h^{-1})	selectivity (%)							
						3	**4**	**3**	**4**	**3**	**4**	**5**	**6**
		0.5 h	1 h	3h		0.5 h [b]		1 h [b]		3 h			
1	dppm	26	47	64	0.60	100	0	80	20	44	48	4	4
2	dppe	65	65	66	2.10	0	85	0	85	0	84	0	16
3	dppp	70	74	80	2.41	35	47	24	52	2	69	4	25
4	dppb	19	44	58	0.42	100	0	100	0	83	13	4	0

[a] Reaction conditions: ratio 4-*tert*-butylphenol/allyl alcohol/[Ru]/AgOTs/HOTs = 1000/1000/1/2/2, toluene, 100 °C (reaction shown in Scheme 1)
[b] in the cases that **3** and **4** do not add up to 100, the remainder is product **5** and **6**

Table 2.6. Reactivity of **3** in the presence of various catalysts [RuCp(PP)](OTs) and added HOTs.[a]



3

entry	RuCp (PP) PP=	conversion of **3** (%)		selectivity (%)[b]			
		1 h	3 h	**1**	**4**	**5**	**6**
1	dppm	7	17	28	36	21	15
2	dppe	79	88	26	42	6	26
3	dppp	86	97	26	45	3	26
4	dppb	2	2	1	99	0	0

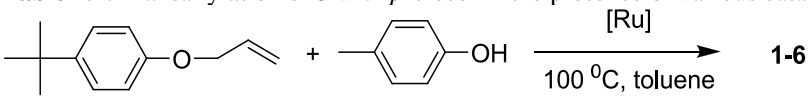
[a] Reaction conditions: ratio **3**/[Ru]/AgOTs/HOTs = 1000/1/2/2, 100 °C
[b] after 3 h

2.2.5 Catalyst Performance vs. Catalyst Structure

The effect of acid addition was also studied for CpRu(PP) complexes in the direct allylation of 1 with 2 (Table 2.5; to be compared to Table 2.3). The product development graphs for the reactions given in Table 5 are given in the Supporting Information. The rate of the allylation reaction for all four catalysts is strongly enhanced by the addition of two equivalents of HOTs (Table 2.5). The effect of acid on the selectivity of the reaction is not the same for all catalysts. For [RuCp(dppe)](OTs) and [RuCp(dppp)](OTs) the selectivity shifts towards C-allylation. Unexpectedly, for [RuCp(dppm)](OTs), O-allylation becomes favored, with an initial selectivity of 100% for **3** after 30 min. Surprisingly, also [RuCp(dppb)](OTs) becomes active for O-allylation. The isomerization of allyl alcohol into propanal, observed with this catalyst under neutral conditions, is apparently blocked by addition of acid. This latter observation could be rationalized by the fact that the formation of a Ru(II)-allyl alcoholate intermediate, being the first step in the isomerization reaction,[12] is suppressed in acidic conditions.

The reaction of **3** into **1–6** with these four catalysts in the presence of added HOTs was also investigated (Table 2.6). [RuCp(dppm)](OTs) shows only low conversion of **3** into C-

Table 2.7. Transallylation of **3** with *p*-cresol in the presence of various catalysts [RuCp(PP)](OTs).[a]



entry	RuCp (PP) PP=	Conversion of **3** (%)				selectivity (%)[b]	
		1 h	3 h	**1**	**4**	**5**	**6**
1	dppm	0	0	-	-	-	-
2	dppe	99	99	50	50	0	0
3	dppp	80	91	50	50	0	0
4	dppb	19	49	49[c]	0	0	0

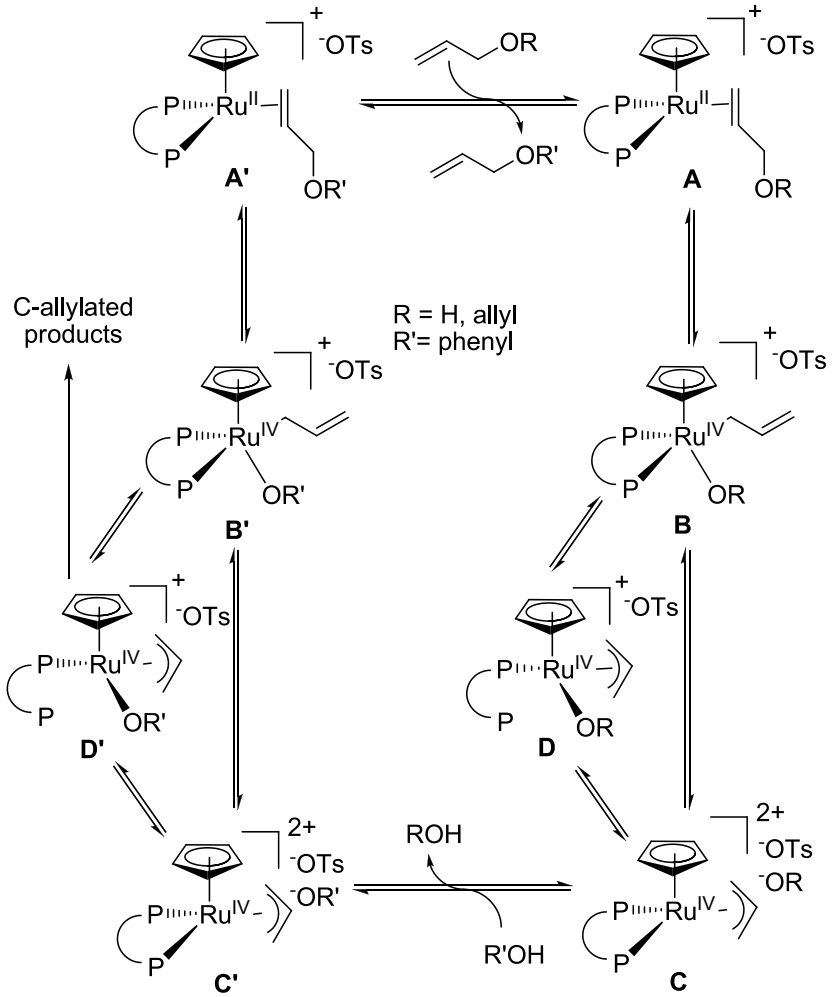
[a] Reagents and conditions: ratio **3**/ *p*-cresol/[Ru]/AgOTs = 1000/1000/1/2, 100 °C
[b] after 3 h; yields are total of both *tert*-butylphenol and *p*-cresol derived products
[c] remaining 51% = *t*-Buphenyl and *p*-cresyl allyl ethers

allylated products, while [RuCp(dppb)](OTs) appears to be hardly active at all. In contrast, [RuCp(dppe)](OTs) and [RuCp(dppp)](OTs) are very active for the conversion of **3** to C-allylated products.

The apparent unreactivity of **3** with [RuCp(dppm)](OTs) and [RuCp(dppb)] (OTs), prompted us to investigate the transallylation of **3** with *p*-cresol in the absence of additional acid (Table 2.7). For [RuCp(dppm)](OTs) the reactivity is extremely low. As expected, [RuCp(dppe)](OTs) and [RuCp(dppp)](OTs) behave very similar to [RuCp(*o*-EtOdppe)](OTs) and rapidly produce a large quantity of C-allylated products. Surprisingly, [RuCp(dppb)](OTs) in the presence of acid is quite active in the transallylation of **3** with *p*-cresol, but is only producing O-allylated products. Apparently, for this catalyst C-allylation is blocked; only after longer reaction times (6–18 h) do C-allylated products slowly appear. Apparently, the result from Table 2.6, entry 4, should be interpreted such that this catalyst is reactive with **3**, but rapidly regenerates it again in the absence of other phenol moieties.

2.2.6 Mechanistic Considerations

It is well-known that the activation of allyl-X (X= halide, carboxylates, alkoxide, etc) substrates by $L_2CpRu(II)X$ complexes in allylation reactions proceeds via oxidative addition to give intermediate $L_nCpRu(IV)(allyl)X_2$ complexes (n=1 for σ-allyl, n=0 for π-allyl).[21] The initially formed product of oxidative addition appeared to be a s-allyl species which only after dissociation of a phosphine or CO ligand converted into the thermodynamically more stable π-allyl species. Reasoning along these lines with allyl alcohol as substrate in the present study, its oxidative addition in [Ru(II)Cp(PP)(allyl alcohol)](OTs) (Scheme 2.2, **A**, R = H) will initially produce [(PP)CpRu(IV)(σ-allyl)OH](OTs) (**B**, R = H). When σ- to π-allyl rearrangement occurs, to prevent a 20- electron species either a p-allyl dicationic complex (**C**)

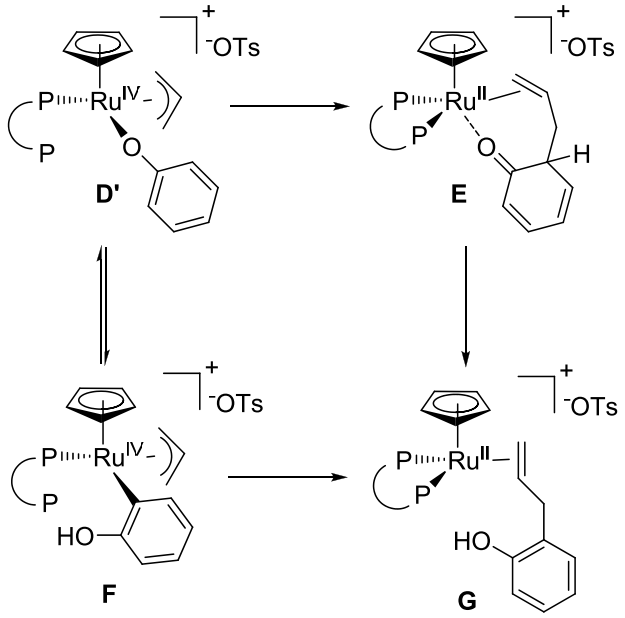


Scheme 2.2. Proposed catalytic cycle for allylation. **B**, **C**, **D** (R = H, allyl) and **B'**, **C'**, **D'** (R = phenyl) are isomeric 18-electron species formed after oxidative addition.

is formed, or a phosphine must dissociate (**D**). Displacement of the hydroxide anion by phenolate in an acid-base reaction from species **C** will be fast and results in the species [(PP)CpRu(IV)(π-allyl)](phenolate)(OTs) (**C'**, R'= Ph) while H_2O is coproduced. Due to the coordinating nature of the phenolate anion, strongly attracted to the positively charged Ru(IV), either species **B'** or **D'** will be formed. After reductive elimination, Ru(II)-bound product is obtained (**A'**) or C-allylated products are irreversibly formed. Complexes of type **B**, **C** and **D** must play a central role in the reaction network of all possible allylation reactions. A third possibility is reductive elimination of the phenyl allyl ether **3** from **B'**, **C'** or **D'** (R'= Ph), a step that is also reversible. The final option is the irreversible formation of the C-allylated product **4**. Likewise, the products **5** and **6** can be formed starting from **4** and allyl alcohol. When **4** is present in a significant concentration, exchange of phenolates could occur in intermediates **B'**, **C'** and **D'**. The occurrence of exchange also rationalizes the observations in Table 2.4 and Table 2.6 that reaction products **5** + **6** are produced in stoichiometric amounts on **1**; these products can only be formed when phenolate **1** is exchanged for

phenolate **4**, regenerating **1** in the process. Since the O-allylation steps all are reversible while formation of the C-allylated products is irreversible, all initially formed phenyl ether products can thus eventually be converted, if a sufficient amount of **2** is available, into fully C-allylated product **6** as is observed after long reaction times (e.g., 18 h).

A σ-π allyl interconversion of the (PP)CpRu(IV)allyl phenolate complex (Scheme 2, **B'**, for R'= Ph) will be dependent on the chelating strength of PP, which is expected to decrease in the order dppp > dppe > dppm. O-Allylated product **3** will be formed from **B'** (for R'=Ph) in a microscopic analogous reverse of the oxidative addition of allyl alcohol **2** to complex **A'** (for R'=Ph). However, C-allylation is generally thought to proceed via π-allyl species. For instance, C-allylation catalyzed by $[Cp^*Ru(IV)(MeCN)_2(\pi\text{-allyl})]^{2+}$ complexes was proposed to proceed via Friedel–Crafts-type attack of the π-allyl moiety of these strongly electrophilic complexes at phenol.[11] Based upon the observed dependence of the allylation selectivity on the structure of the applied phosphine bidentate ligand and its chelating strength, a hypothesis that C-allylation also requires activation of the phenol via its O-atom at ruthenium is favored (Scheme 2.3). If the isomeric π-allyl species **C'** and **D'** are more abundantly present, due to weak chelation or space around ruthenium, reductive elimination of O-allylated product will be relatively slow, as this proceeds via the s-allyl intermediate **B'**. It is proposed that C-allylated products are formed starting from intermediate **D'** (Scheme 2.3). The mechanism could proceed via an intramolecular Friedel–Crafts reaction, in which the phenolate ring has to reorientate in the same plane as the allyl group, and for which sufficient space around



Scheme 2.3. Proposed mechanism for C-allylated products via either Friedel-Craft or *ortho*-metallation.

ruthenium is needed, forming species **E** (Scheme 2.3). After tautomerization the C-allylated product is formed (**G**). Another mechanism could proceed via an ortho-metallation-type reaction, for which space around ruthenium is also required in order to activate the C-H bond, forming species **F**; after reductive elimination species **G** is then formed.

2.2.7 Effect of the Acid

The working hypothesis is thus summarized: more free coordination space at Ru is required for C-allylation. Therefore weakly chelating and/or small bite angle phosphine ligands give more selective catalysts for C-allylation, whereas stronger chelating, and/or larger bite angle ligands give catalysts which show higher selectivity for O-allylation. The rate-determining step in the allylation reaction with allyl alcohol is generally proposed to involve the oxidative addition of allyl alcohol, as OH is considered to be a poor leaving group.[11] Often intermediate protonation of allyl alcohol is implicated to increase the reactivity of allyl alcohol for allylation reactions.[10,11,22,23] The strong increase in allylation reaction rate observed with addition of a catalytic quantity of a strong acid such as HOTs (Table 2.5), can thus be explained by protonation of the allyl alcohol, making H_2O the better leaving group. By the same reasoning, the protonation of the allyl ether **3** at the phenoxy group, makes the phenol a good leaving group, thus rationalizing the promoting effect of acid on the rate of activation of allyl ether **3** (Table 2.6). A strongly electrophilic, dicationic $[(PP)CpRu(IV)(\pi\text{-allyl})]^{2+}$ species (type **C**) is created and phosphine dissociation is not necessary to form the stable, resting state π-allyl species. Phenol may assist in the oxidative addition, perhaps as a proton donor or otherwise in hydrogen bonding and a concerted mechanism, as is clear from the transallylation results shown in Table 2.4. However, the oxidative addition also occurs in the presence of much weaker acids, such as 1-octanol. In both cases, the addition of a strong acid results in a strongly increased rate of reaction. The dramatic change in the reactivity of the catalyst $[RuCp(dppb)]^+$ upon addition of acid is indicative of a change in the formed intermediate. It has been reported that oxidative addition of allyl alcohol in the absence of acid does take place, the reaction medium becoming more basic,[24] which supports our theory on initial hydroxyl anion formation. The microscopic reverse of the acid-catalyzed oxidative addition of phenyl allyl ether, that is, the formation of **3** by coordination of phenol to the Ru(IV) centre via (concerted) deprotonation and reductive elimination of **3** is expected to be more facile and thus occurs with higher rate in the presence of acid. As the rates of the reactions shown in Scheme 2.3 towards either species **E** or **F** are expected to be relatively

insensitive to acid, it can be rationalized that even with small bite angle dppm as well as the large bite angle ligand dppb an increased selectivity for O-allylation is observed in the presence of a catalytic quantity of acid. However, the cause of this increased selectivity is different for the two catalysts. While [RuCp(dppm)](OTs) undergoes the oxidative addition of allyl alcohol with a slightly higher rate than that of **3** (still being slow for both), [RuCp(dppb)](OTs) performs the oxidative addition of **3** in a higher rate, however, it is hardly able to produce C-allylated products. The complexes [RuCp(dppe)](OTs) and [RuCp(dppp)](OTs) react in such a high rate, that whereas oxidative addition of **3** as well as the reductive elimination to **3** has become more facile, the high rate of C-allylation with these catalysts makes that the reaction rapidly proceeds to the thermodynamic sink of C-allylated products.

2.3 Conclusions

In summary, a catalytic system has been developed that can catalyze both O- as well as C-allylation of phenols, without the need of any stoichiometric amounts of additives. It was shown that the O-allylated products are reversibly formed, while C-allylated products are produced irreversibly. Small quantities of an acid can fulfil a strong rate-promoting role. It is proposed that protons strongly reduce the activation barriers for oxidative addition and reductive elimination at the RuCp(PP) centre, for both of the substrate allyl alcohol as well as product allyl ether compounds. It has been unambiguously demonstrated that a Ru-catalyzed conversion of O-allylated products to the thermodynamically more favourable C-allylated products may readily occur under allylation conditions. Thus, C-allylated products can ultimately be catalytically produced in high yield by allylation of phenols with allyl alcohol. The efficiency of the consecutive C-allylation is, however, strongly dependent on the structural characteristics of the Ru complex as appears from the results given in Table 2.3. It appears that restricted coordination space at the ruthenium centre favours the formation of the O-allylated product, while sufficient space, either due to weak chelation and/or small bite angle, favours C-allylation. The addition of catalytic amounts of acid strongly promotes the rate of the reaction. The chelate strength plays a less dominant role in the acidic system, because the bidentate phosphine is less likely to dissociate and thus the bite angle seems to be determining selectivity.

2.4 Experimental

General remarks. All reactions were performed under an argon atmosphere using standard Schlenk techniques. Solvents were dried and distilled by standard procedures and stored under argon. The phosphine ligands dppm, dppe, dppp, dppb, dcpe, and triphenylphosphine were commercially available and used as received. The synthesis of the substituted phosphine ligands *o*-MeOdppm,[25] *o*-MeOdppe,[26] *o*-MeOdppp,[27] and *o*-EtOdppe[28] has been previously reported in literature. $RuCl_3.3H_2O$ (Johnson & Matthey) was used as received. [RuCpCl(PPh_3)$_2$],[14] [RuCpCl(dcpe)],[29] [RuCpCl(dppm)],[15] [RuCpCl(dppe)],[16] [RuCpCl(dppp)], [RuCpCl(dppb)],[30] [and [RuCpCl(*o*-MeOdppe)][12] were prepared according to literature procedures. C,H,N,S analyses were performed on a Perkin Elmer 2400 Series II analyzer.

NMR Experiments. ^{1}H NMR spectra (300 MHz), and ^{31}P{^{1}H}NMR spectra (121.4MHz) were measured on a Bruker DPX-300. Chemical shifts are reported in ppm. Proton chemical shifts are relative to TMS, and phosphorus chemical shifts are relative to 85% aqueous H_3PO_4. The spectra were taken at room temperature.

General procedure for RuCpCl(PP) synthesis. A solution of RuCpCl(PPh_3)$_2$ (72 mg, 0.1 mmol) and the bidentate phosphine ligand (0.1 mmol) in 5 ml toluene was stirred for 16 h at 90 °C. The solution was cooled to room temperature and flushed over a column of silica gel (3 g, d = 1 cm) with 15 ml of toluene to remove the triphenylphosphine. Finally, the orange product was eluted with ethyl acetate until the eluents was colorless. The solution was then concentrated in *vacuo* to approximately 1 ml and the product precipitated with petroleum ether.

RuCpCl(*o*-EtOdppe) was obtained as a yellow / orange solid in a yield of 63 mg (81%). Crystals suitable for X-ray diffraction were obtained by slow diffusion of n-hexane into a solution of the complex in toluene. Anal. Calcd for $C_{39}H_{45}ClO_4P_2Ru\cdot0.5$(toluene): C, 62.07; H, 6.01. Found: C, 61.76; H, 5.99. ^{1}H-NMR ($CDCl_3$): δ 8.20-8.11 (m, 2H, ArH), 7.24-7.17 (m, 4H, ArH), 6.99 (t, 2H, *J* = 7 Hz, ArH), 6.96 (bs, 2H, ArH), 6.69-6.61 (m, 6H, ArH), 4.56 (s, 5H, Cp), 3.69-3.56 (m, 8H, OCH_2), 2.63 (m, 4H, CH_2), 0.85 (t, 6H, *J* = 7 Hz, CH_3), 0.77 (t, 6H, *J* = 7 Hz, CH_3). ^{31}P{^{1}H}-NMR ($CDCl_3$): δ 68.1.
RuCpCl(*o*-MeOdppm) was obtained as an orange solid in a yield of 58 mg (82%). Crystals suitable for X-ray diffraction were obtained by slow diffusion of n-hexane into a solution of the complex in toluene. Anal. Calcd for $C_{34}H_{35}ClO_4P_2Ru\cdot1.5$(water): C, 53.94; H, 5.06. Found: C, 54.09; H, 4.96. ^{1}H-NMR ($CDCl_3$): δ 8.05 (d, 2H, *J* = 5 Hz, ArH), 7.60-7.54 (m, 4H, ArH), 7.28-7.14 (m, 4H, ArH), 6.96-6.75 (m, 6H, ArH), 4.50 (s, 5H, Cp), 3.65 (s, 6H, OMe), 3.62 (s, 6H, OMe), 2.77 (s, 2H, CH_2). ^{31}P{^{1}H}-NMR (acetone-d_6): δ 4.1.
RuCpCl(*o*-MeOdppp) was obtained as a yellow solid in a yield of 52 mg (71%). Crystals suitable for X-ray diffraction were obtained by slow diffusion of n-hexane into a solution of the complex in toluene. Anal. Calcd for $C_{36}H_{39}ClO_4P_2Ru\cdot1.33$(toluene): C, 63.53; H, 5.84. Found: C, 63.90, H, 5.39. ^{1}H-NMR ($CDCl_3$): δ 7.36-7.29 (m, 4H, ArH), 7.04-6.99 (m, 4H, ArH), 6.82 (t, 4H, *J* = 7 Hz, ArH), 6.65-6.61 (m, 4H, ArH), 4.28 (s, 5H, Cp), 3.36 (s, 6H, OMe), 3.27 (s, 6H, OMe), 2.8-2.4 (br m, 6H, CH_2). ^{31}P{^{1}H}-NMR (acetone-d_6): δ 40.2.

General procedure for catalytic reactions. 5 mmol of 4-*tert*-butylphenol (or in some experiments 4-*tert*-butylphenyl allyl ether), 0.005 mmol of the ruthenium complex, 0.01 mmol of AgOTs and, if indicated, 0.01 mmol of additive were charged into the reaction vessel

and flushed with argon. Degassed and dried toluene was added (5 ml) and the mixture was stirred for five minutes. Allyl alcohol (or diallyl ether) was added (5-10 mmol) and the reaction was stirred for 3 hours at 100 °C. Samples were taken at certain time intervals with an airtight syringe and analyzed by gas chromatography. To isolate and characterize compounds **3-6**, preparative HPLC purification was performed for selected experiments; the isolated yields corresponded with the yields found by GC. The NMR and mass spectra of the products **3**-**6** were in agreement with the data found in literature.[31]

GLC method. Quantitative gas liquid chromatography analyses were carried out on a Varian CP-3800 apparatus equipped with a VF-1ms (25 m × 0.25 mm) column with decane as internal standard. The temperature gradient used was: isothermal for 5 minutes at 40 °C, heating 10 °C/ minute to 250 °C and finally isothermal for 5 minutes at 250 °C.

X-ray crystal structure determinations. X-ray intensities were measured on a Nonius Kappa CCD diffractometer with rotating anode (graphite monochromator, $\lambda = 0.71073$ Å) up to a resolution of $(\sin\theta/\lambda)_{max} = 0.65$ Å^{-1} at a temperature of 150 K. The structures were solved with automated Patterson methods (program DIRDIF-99[32]). Refinement was performed with

Table 2.8. Crystal data and structure refinement for the complexes RuCpCl(*o*-EtOdppe), RuCpCl(*o*-MeOdppm) and RuCpCl(*o*-MeOdppp).

	RuCpCl(*o*-EtOdppe)	**RuCpCl(*o*-MeOdppm)**	**RuCpCl(*o*-MeOdppp)**
formula	$C_{39}H_{45}ClO_4P_2Ru$	$C_{34}H_{35}ClO_4P_2Ru \cdot C_7H_8$ + disordered solvent	$C_{36}H_{39}ClO_4P_2Ru$
fw	776.21	798.21 [*]	734.13
crystal colour	orange	orange	yellow
crystal size [mm^3]	0.21 x 0.15 x 0.12	0.30 x 0.27 x 0.24	0.30 x 0.15 x 0.12
crystal system	orthorhombic	triclinic	triclinic
space group	$Pna2_1$ (no. 33)	$P\bar{1}$ (no. 2)	$P\bar{1}$ (no. 2)
a [Å]	26.5195(11)	12.14373(15)	10.08714(17)
b [Å]	12.5266(2)	13.22525(15)	11.00266(14)
c [Å]	11.0325(4)	14.98261(17)	15.7896(3)
α [°]	-	66.472(1)	73.742(1)
β [°]	-	79.779(1)	85.868(1)
γ [Å^3]	-	65.088(1)	80.460(1)
V [Å^3]	3665.0(2)	2000.82(5)	1658.47(5)
Z	4	2	2
D_x [g/cm^3]	1.407	1.325 [*]	1.470
μ [mm^{-1}]	0.627	0.576 [*]	0.688
abs. corr. method	none	multi-scan	multi-scan
abs. corr. range	-	0.69 – 0.87	0.70 – 0.92
refl. (meas./unique)	41239 / 8439	27030 / 8759	24452 / 7567
param./restraints	439 / 3	466 / 0	421 / 0
R1/wR2 [I>2σ(I)]	0.0498 / 0.0861	0.0287 / 0.0801	0.0227 / 0.0520
R1/wR2 [all refl.]	0.0859 / 0.0999	0.0321 / 0.0822	0.0283 / 0.0541
S	1.105	1.050	1.069
Flack parameter	-0.06(4)	-	-
$\rho_{min/max}$ [e/Å^3]	-0.72 / 0.88	-0.79 / 0.95	-0.47 / 0.37

[*] Derived parameters do not contain the contribution of the disordered solvent.

SHELXL-97[33] against F^2 of all reflections. Geometry calculations, illustrations, and checking for higher symmetry was performed with the PLATON program.[34]
The crystal of [RuCpCl(*o*-EtOdppe)] was cracked into two fragments. The orientation matrices of both fragments were taken into account during intensity integration with the program EvalCCD.[35] Refinement was performed on a HKLF5 file.[36] Hydrogen atoms were introduced in calculated positions and refined with a riding model. One ethyl group was refined with a disorder model.
The crystal of [RuCpCl(*o*-MeOdppm)] contained large voids (211.6 $Å^3$ / unit cell) filled with disordered solvent molecules. Their contribution to the structure factors was secured by back-Fourier transformation using the SQUEEZE routine of the program PLATON,[34] resulting in 22 electrons / unit cell. Hydrogen atoms were introduced in calculated positions. The hydrogen atoms of the Cp-ligand were refined freely with isotropic displacement parameters; all other hydrogen atoms were refined with a riding model.
In [RuCpCl(*o*-MeOdppp)] hydrogen atoms were introduced in calculated positions. The hydrogen atoms of the Cp-ligand were refined freely with isotropic displacement parameters; all other hydrogen atoms were refined with a riding model. Relevant crystal structure and refinement data are provided in Table 2.8.

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3

[RuCp(PP)]$^+$-catalyzed allylation of phenols: a gem-dialkyl-type effect induces high selectivity for O-allylation

Abstract
It appears that catalysts containing bidentate phosphine ligands having geminal dialkyl substituents at the central atom of a C_3-bridging group of the phosphine ligand are highly selective for O-allylation of phenol with allyl alcohol; apparently the presence of the substituents efficiently blocks the competitive and thermodynamically more favorable pathway to C-allylation. It appears that the electronic and structural properties of the Ru(II) precursor complexes in the solid state do not differ significantly from those of complexes containing unsubstituted analogous ligands, while the resulting catalysts show a vastly different catalytic performance. The results suggest that the geminal dialkyl substitution at the central carbon of the C_3-bridge of the ligand primarily leads to an increased kinetic stability of the bidentate chelate under reaction conditions, such as in the proposed intermediate [Ru(IV)Cp(diphosphine)(allyl)]$^{2+}$ complexes. This implies that the high kinetic stability of the diphosphine chelate bound to Ru blocks the pathway to the thermodynamically favored C-allylation product. The results provide an interesting example in which the application of the geminal dialkyl substitution in the bridge of a bidentate ligand serves as a diagnostic tool to probe the nature of the selectivity-determining step in a catalytic pathway in homogeneous catalysis.

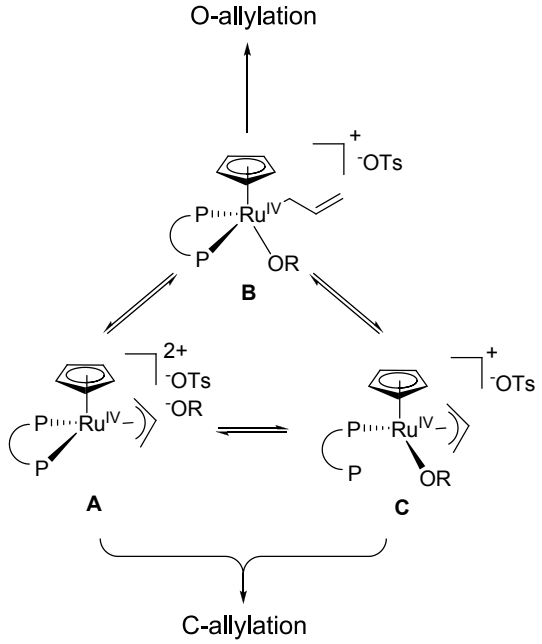
This Chapter is based on: J.A. van Rijn, M.A. Siegler, A.L. Spek, E. Bouwman, E.Drent, Organometallics 2009, 28, 7006-7014.

3.1 Introduction

Selective O-allylation of phenols is a highly desired reaction in the development of a environmentally benign synthesis of epoxy resins on a industrial scale.[1] Catalytic O-allylation of phenols is most frequently reported using allylating agents with good leaving groups such as allyl chloride or allyl acetate and stoichiometric amounts of base are added to induce good selectivity;[2-4] these processes thus all result in stoichiometric saline waste. From an atom-efficiency point of view it would be desirable to use allyl alcohol as allylating agent, forming only water in the process. An example of selective O-allylation of phenol with allyl alcohol was demonstrated using a palladium catalyst in the presence of stoichiometric amounts of the base ($Ti(OiPr)_4$.[5] In an industrial application this would lead to a vast quantity of Ti-salt waste, which is clearly undesired. In the absence of the Ti-salt, however, such a catalytic system leads to C-allylation.[6] Also with the Ru(IV) catalyst precursor described by Pregosin and co-workers,[7] phenols are exclusively C-allylated.

In Chapter 2, a [RuCp(diphosphine)]-based catalytic system is described that catalyzes both O- and C-allylation of phenols with allyl alcohol, without the need of any stoichiometric amounts of additives. It was shown that formation of O-allylated products is equilibrium limited, while C-allylated products are produced irreversibly as the thermodynamically favored product. It was also found that the addition of a catalytic quantity of a Brønsted acid has a major effect on the rate of allylation as well as the course of the reaction. A triplet of isomeric Ru(IV)Cp(PP)(allyl)(OR)(OTs) intermediates formed after oxidative addition of either allyl alcohol or allyl phenyl ether at [Ru(II)Cp(PP)](OTs) are believed to play a key role in determining the selectivity of the allylation reaction (Scheme 3.1). As the desired product is formed in an equilibrium reaction, it implies that it is not useful to discuss this reaction in terms of yields. In an industrial process, however, this type of reaction may be applied with recycling of the reactants, for which especially high selectivity is important.

It is thought that, next to the 18-electron σ-allyl species **B,** both π-allyl species **A** and **C** can be reversibly accessed. To prevent a 20-electron species, it is proposed that either the RO^- anion is expelled from the coordination sphere (**A**), or that phosphine dissociation will occur (**C**). From the observed catalyst structure- performance relationship of the Ru catalysts it is concluded that the availability of space around the ruthenium center is an important factor in determining the course of the allylation reaction (Chapter 2). It is suggested that it could be species **C** that provides sufficient space at the Ru(IV) center to accommodate the apparently



Scheme 3.1. Proposed intermediates in the catalytic allylation of phenol with allyl alcohol.

space-demanding transition state towards C-allylation, while competitive reductive elimination from species **B** would produce the desired allyl ether (Chapter 2).

Dissociation of one phosphorus donor of the bidentate phosphine ligand could thus be a possible event to create the necessary space at the ruthenium center to open up the pathway towards C-allylation. Alternatively, the sterics of the chelating diphosphine ligand itself – and not its partial dissociation – could also be a crucial factor determining the competition between O-allylation and C-allylation involving species of type **A** and **B**. In the present work, experiments are described that will allow us to discriminate between either ligand dissociation or its sterical demands as a chelating ligand, in the crucial selectivity-determining step in the catalytic cycle. A series of complexes with chelating bidentate phosphine ligands with a focus on backbone variation (Figure 3.1) was tested for their activity and selectivity in the allylation of phenol with allyl alcohol. The ligands, with bridging groups ranging from C_1 to C_3, all have substitution on the ligand backbone and were selected to investigate if ligand dissociation and/or the ligand sterical demands determine selectivity in this reaction by comparing them with their unsubstituted analogues (Chapter 2).

3.2 Results and discussion

3.2.1 Synthesis

The catalyst precursor complexes [RuCpCl(PP)] with the ligands shown in Figure 3.1 were synthesized using a procedure reported in Chapter 2. It was found that formation of the

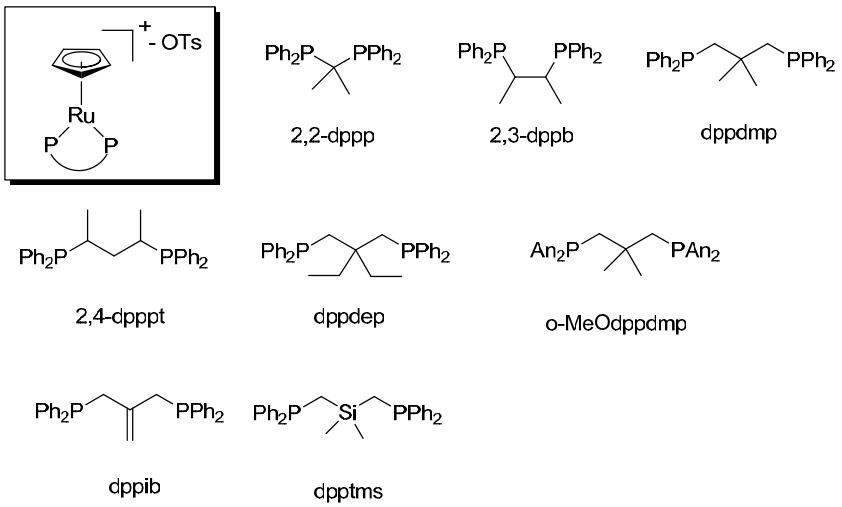


Figure 3.1. Schematic overview of the catalytic ruthenium complexes with the employed bidentate phosphine ligands and their abbreviations (An = *o*-anisyl).

complexes with ligands containing a substituted bridge generally requires longer reaction times than those with unsubstituted ligands (16 vs 6 hours). A striking feature of the new complexes is their high stability in solution in air. Whereas [RuCpCl(PP)] complexes of diphosphines with unsubstituted alkylene bridges rapidly decompose in solution when exposed to air, these novel complexes are stable for several weeks on the bench and crystals can even be grown in air. The yields of the syntheses were high and all complexes have been characterized by elemental analysis, ^{1}H-NMR and ^{31}P-NMR spectroscopy. In the complexes with *geminal* substitution, the two alkyl substituents on the central carbon in the bridge are non-equivalent with respect to the Cp ring; separate signals are detected in ^{1}H-NMR.

The phosphorus resonances of the complexes with the *geminal* disubstituted C_3-ligands are very similar to that of unsubstituted complexes, i.e. [RuCpCl(dppp)] and [RuCpCl(dppdmp)] both show a ^{31}P-NMR resonance around +40 ppm, indicating that the ligand binding properties to Ru(II) in these complexes hardly change by substitution at the central carbon of the C_3-bridging group. Also the complex [RuCpCl(dppib)], in which dppib can be viewed as a special geminally substituted C_3-diphosphine ligand, shows a similar resonance in ^{31}P-NMR (43.0 ppm). On the other hand, for [RuCpCl(2,4-dpppt)] (1,3-disubstitution of the C_3-bridge) the ^{31}P-NMR spectrum shows a significant shift (to 51.8 ppm). Geminal dialkyl substitution of the ligand with a C_1-bridging group has a significant effect on the ligand binding properties, as indicated by the ^{31}P-NMR chemical shift of 43.0 ppm for [RuCpCl(2,2-dppp)] vs 15.7 ppm for [RuCpCl(dppm)]. Alkyl substitution at a C_2-bridging group leads to a less dramatic effect on the ^{31}P NMR resonances: i.e. 86.0 ppm for [RuCpCl({S,S}-2,3-dppb)] versus 80.1 ppm for [RuCpCl(dppe)].

3.2.2 Crystal structures

Crystals of [RuCpCl(dppdep)], [RuCpCl(dppdmp)], [RuCpCl(dpptms)], [RuCpCl(*o*-MeOdppdmp)] and [RuCpCl(2,2-dppp)] were obtained by slow diffusion of n-hexane into solutions of the complexes in toluene. Selected bond distances and angles are listed in Table 3.1.

The asymmetric units of [RuCpCl(*o*-MeOdppdmp)] and [RuCpCl(2,2-dppp)] contain two independent molecules; distances and angles are given in Table 3.1 for only one of the

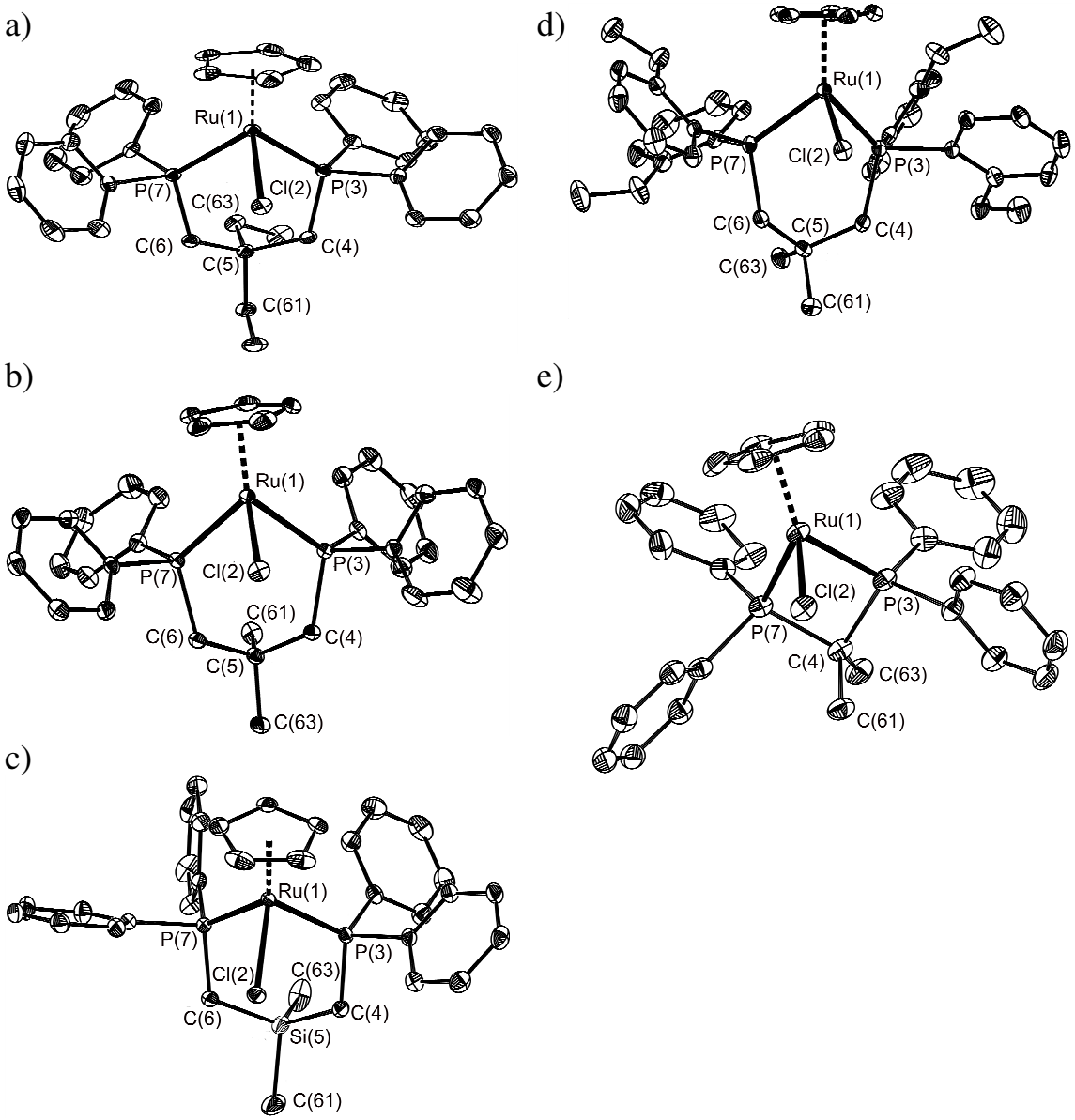


Figure 3.2. Displacement ellipsoid plots (50% probability level) of one formula unit of a) [RuCpCl(dppdep)], b) [RuCpCl(dppdmp)], c) [RuCpCl(dpptms), d) [RuCpCl(*o*-MeOdppdmp)] and e) [RuCpCl(2,2-dppp)]. For [RuCpCl(dppdep)], the minor component of the disordered Cp ligand and the lattice disordered toluene molecule are omitted for clarity. For [RuCpCl(*o*-MeOdppdmp)] and [RuCpCl(2,2-dppp)], only one of the two independent molecules is shown. H-atoms are omitted for the sake of clarity.

Table 3.1. Selected bond lengths (Å) and angles (°) for the complexes [RuCpCl(dppdep)], [RuCpCl(dppdmp)], [RuCpCl(dpptms)], [RuCpCl(*o*-MeOdppdmp)] and [RuCpCl(2,2-dppp)].

	[RuCpCl (dppdep)]	[RuCpCl (dppdmp)]	[RuCpCl (dpptms)]	[RuCpCl(*o*-MeOdppdmp)]	[RuCpCl(2,2-dppp)]
Bond distances (Å)					
Ru(1)-Cl(2)	2.4370(5)	2.4443(4)	2.4384(3)	2.4512(9)	2.4259(8)
Ru(1)-P(3)	2.2820(5)	2.2984(4)	2.2749(4)	2.2891(10))	2.2890(6)
Ru(1)-P(7)	2.2817(4)	2.2668(4)	2.3028(3)	2.2619(10)	2.2620(6)
Ru(1)-Cp	1.852(2)	1.8608(8)	1.8524(7)	1.8494(18)	1.867(2)
Angles (°)					
P(3)-Ru(1)-P(7)	91.946(16)	92.078(15)	93.869(13)	91.09(3)	71.54(2)
P(3)-Ru(1)-Cl(2)	84.29(2)	82.435(14)	87.419(12)	87.34(3)	91.08(2)
P(7)-Ru(1)-Cl(2)	83.75(2)	85.078(14)	88.118(12)	87.10(3)	95.41(2)
C(4)-C(5)-C(6)	111.31(13)	111.19(12)	-	114.7(3)	-
C(4)-Si(5)-C(6)	-	-	110.29(6)	-	-
P(3)-C(4)-P(7)	-	-	-	-	89.37(9)
C(61)-C(5)-C(63)	108.89(14)	108.71(13)	-	106.8(3)	-
C(61)-Si(5)-C(63)	-	-	108.71(9)	-	-
C(61)-C(4)-C(63)	-	-	-	-	109.35(19)

independent molecules as the structural parameters are very similar. The displacement ellipsoid plots of [RuCpCl(dppdep)], [RuCpCl(dppdep)], [RuCpCl(dpptms)], [RuCpCl(*o*-MeOdppdmp)] and [RuCpCl(2,2-dppp)] are shown in Figure 3.2.

The distances of the ruthenium center to the cyclopentadienyl group, the phosphorus atoms and the chloride anion are quite similar for all five compounds and are comparable to related ruthenium complexes (Chapter 2).[8-11] The effects of the backbone substituents on the overall solid state structure are rather small; especially the bite angle of the diphosphine ligand hardly changes (92.591(15)° and 91.09(3)° for [RuCpCl(*o*-MeOdppp)] (Chapter 2) and [RuCpCl(*o*-MeOdppdmp)], respectively). Also no significant difference in the angle C(4)-C(5)-C(6) between these two compounds is present (115.32(14)° *vs* 114.7(3)°). When the substituents are changed from methyl to ethyl groups, a change in angles is foreseen; however, for [RuCpCl(dppdep)] and [RuCpCl(dppdmp)] neither the bite angle (91.946(16)°) vs 92.078(15)°) nor the C(4)-C(5)-C(6) angle (111.31(13)° vs 111.19(12)°) are significantly changed.

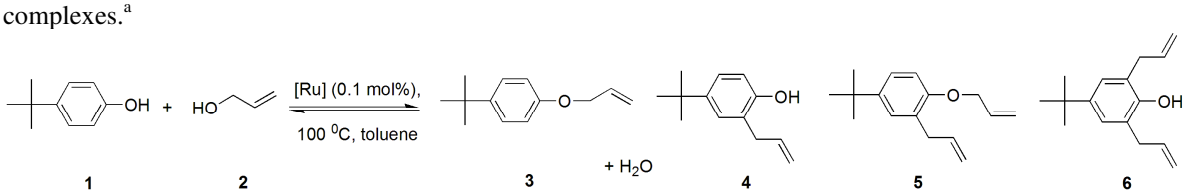
Also for C_1-bridged complexes, where the bite angle is expected to be more directly influenced by introduction of substituents, the difference between [RuCpCl(dppm)][9] and the dimethyl-substituted [RuCpCl(2,2-dppp)] is negligible (72.07(2)° vs 71.60(2)°). A potential angle compression due to the presence of the (geminal) substituents is thus not reflected in the solid-state structures of the Ru(II) complexes.

3.2.3 Catalysis

The catalytic activity of the ruthenium complexes with methyl substituents on the ligand backbone in the allylation of 4-*tert*-butylphenol with allyl alcohol was investigated; the results are shown in Table 3.2. A catalyst loading of 0.1 mol% was used at a reaction temperature of 100 °C. Apart from the desired O-allylated product **3**, the undesired C-allylated products **4**-**6** are formed, as reported in Chapter 2. The results of the catalytic experiments using the complexes with unsubstituted bidentate phosphine ligands dppm, dppe and dppp are listed in entries 2, 4 and 7 for comparison.

It has been reported in Chapter 2 that the use of both dppm and dppe as the ligand results in very low selectivity for O-allylation (entries 2 and 4), but with completely different activity. The use of dppm yields a catalyst with low activity, while the use of dppe yields a highly active catalyst, resulting in the formation of almost exclusively C-allylated products with high rate. Geminal substitution of the C_1-bridged ligand in [RuCp(2,2-dppp)](OTs) (entry 1) results in an increase in the rate of the reaction as well as the selectivity for O-allylation. Vicinal disubstitution of the C_2-backbone ligand in [RuCp(2,3-dppb)](OTs) (entry 3), however, seems to have no effect on either rate or selectivity (cf entries 3 and 4). On the other hand, complexes with dialkyl substituted C_3-backbones, i.e. [RuCp(dppdmp)](OTs) (entry 5) and [RuCp(2,4-dpppt)](OTs) (entry 6), show a much higher selectivity towards O-allylated product **3** (up to 87%), combined with a somewhat lower catalyst activity, compared to the complex [RuCp(dppp)](OTs) (entry 7). The effect of 1,3-dimethyl substitution of the C_3 backbone for the 2,4-dpppt ligand might perhaps not be too surprising as the methyl

Table 3.2. Reaction of 4-*tert*-butylphenol (**1**) with allyl alcohol (**2**) catalyzed by different $[RuCp(PP)]^+$ complexes.[a]



entry	[RuCp(PP)] (OTs) PP =	conversion of **1** (%)	selectivity for (%) **3**	**4-6**
1	2,2-dppp	44	27	73
2[b]	dppm	21	2	98
3	2,3-dppb	74	4	96
4[b]	dppe	72	4	96
5	dppdmp	30	87	13
6	2,4-dpppt	25	86	14
7[b]	dppp	53	44	56

[a] Reaction conditions: ratio 4-*tert*-butylphenol/allyl alcohol/[RuCpCl(PP)]/AgOTs = 1000/1000/1/2, toluene, 100 °C, 3 h.
[b] Results taken from Chapter 2

Table 3.3. Reaction of 4-*tert*-butylphenol (**1**) with allyl alcohol (**2**) catalyzed by different [RuCp(PP)]$^+$complexes.[a]

entry	[RuCp(PP)] (OTs)	conversion of **1** (%)				selectivity for (%)							
		0.5 h	1 h	3 h	6 h	0.5 h		1 h		3 h		6 h	
	PP =					**3**	**4-6**	**3**	**4-6**	**3**	**4-6**	**3**	**4-6**
1	dppdmp	2	7	30	63	>99	0	>99	0	87	13	82	18
2	dppdep	1	4	20	31	>99	0	>99	0	90	10	88	12
3	*o*-MeOdppdmp	0	0	9	17	-	-	-	-	>99	0	99	1
4	dppib	0	4	26	46	-	-	>99	0	85	15	63	37
5	dpptms	0	2	20	41	-	-	>99	0	99	1	84	16
6[b]	dppp	24	42	53	70	80	20	70	30	44	56	27	73

[a] Reaction conditions: ratio 4-*tert*-butylphenol/allyl alcohol/[RuCpCl(PP)]/AgOTs = 1000/1000/1/2, toluene, 100 °C

[b] results taken from Chapter 2

substituents adjacent to phosphorous will lead to significantly altered stereo-electronic ligand binding characteristics of the diphosphine ligand, as is in fact indicated by the ^{31}P-NMR data. The most intriguing observation from Table 3.2 is that the selectivity for O-allylation of the complex [RuCp(dppdmp)](OTs) (entry 5) compared to [RuCp(dppp)](OTs) is increased in a major way. This is a remarkable observation, as both the ^{31}P-NMR data and the X-ray structures of these Ru(II) catalyst precursors suggest that these ligands impose a very similar stereo-electronic coordination environment at the ruthenium center. Therefore, the catalytic performance of [RuCp(dppdmp)](OTs) and RuCp complexes of other ligands with *geminal* substitution on the central atom of C_3-backbone ligands shown in Figure 3.1 were studied in more detail. Conversions and selectivities as a function of reaction time are shown in Table 3.3.

The complex [RuCp(dppdmp)](OTs) (entry 1) shows a remarkably steady activity while maintaining a high selectivity towards product **3** after longer reaction times. Even after six hours and more than 60% conversion the selectivity for the O-allylated product is relatively high (82%). This is in sharp contrast with the performance of the unsubstituted analogue [RuCp(dppp)](OTs) (entry 6), which rapidly forms increased amounts of C-allylated products over time. Increasing the bulk on the C_3 backbone from methyl to ethyl groups in [RuCp(dppdep)](OTs) (entry 2) results in slightly higher selectivities, but with a somewhat decreased activity of the catalyst. Introduction of *ortho*-methoxy groups on the phenyl rings in [RuCp(*o*-MeOdppdmp)](OTs) (entry 3) results in lower activity compared to [RuCp(dppdmp)](OTs), but with a very high selectivity for O-allylation. For the catalyst with an isobutene bridging group (entry 4) the initial activity and selectivity are comparable to that of [RuCp(dppdmp)](OTs) (entry 1), but after longer reaction times the selectivity for O-allylation deteriorates. The introduction of a silicon atom in the central position of the bridge

Table 3.4. Reaction of 4-*tert*-butylphenol with allyl alcohol catalyzed by different complexes in presence of acid [a]

Entry	[RuCp(PP)](OTs)	conversion of **1** (%)			selectivity (%)					
		0.5 h	1 h	3 h	0.5 h		1 h		3 h	
	PP =				**3**	**4-6**	**3**	**4-6**	**3**	**4-6**
1	dppdmp	46	57	58	83	17	58	42	46	54
2	dppdep	44	58	71	>99	0	90	10	73	27
3	*o*-MeOdppdmp	41	42	48	95	5	95	5	95	5
4	dppib	74	74	78	9	91	2	98	2	98
5	dpptms	39	54	69	90	10	85	15	68	32
6[b]	dppp	70	74	80	35	65	24	76	2	98

[a] Reaction conditions: ratio 4-*tert*-butylphenol/allyl alcohol/[RuCpCl(PP)]/AgOTs/HOTs = 1000/1000/1/2/2, 100 °C.
[b] Results taken from Chapter 2

in [RuCp(dpptms)](OTs) (entry 5) leads to a decrease in activity compared to entry 1, but with a slightly higher selectivity.

3.2.4 Acid effect

In Chapter 2 it has been reported that addition of catalytic quantities of a strong acid to RuCp(PP) catalyst systems, e.g. *p*-toluenesulfonic acid (HOTs), not only significantly increases the activity of the catalysts, but also affects the selectivity. The effect of acid on the activity and selectivity of the catalysts with the dialkyl substituted C_3 ligands was thus investigated in more detail; the results are presented in Table 3.4.

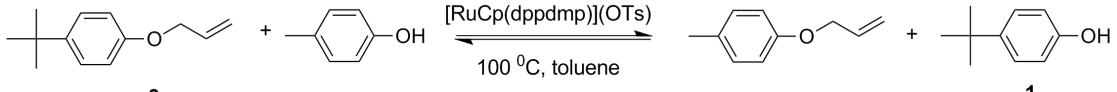
For [RuCp(dppdmp)](OTs) (entry 1, Table 3.4), in the presence of acid the conversion of **1** after 30 minutes is already higher than the conversion after 3 hours without acid (entry 1; Table 3.3). After longer reaction times selectivity towards **3** slowly deteriorates, but in a much lesser extent than observed for the unsubstituted analogue [RuCp(dppp)](OTs) (entry 6). Although conversion hardly increases between 1 and 3 hours, in this time span the selectivity changes, indicating that the catalyst is still active as an allylation catalyst. However, as the product **3** is now present in a higher concentration than allyl alcohol, the catalyst now converts **3** to the thermodynamically-favored products **4**-**6**. For the catalyst with the more bulky bridge-substituted ligand [RuCp(dppdep)](OTs) (entry 2), the increase in rate is even more pronounced, but the selectivity remains higher than that of [RuCp(dppdmp)](OTs). The catalyst [RuCp(*o*-MeOdppdmp)](OTs) in the absence of acid (entry 3; Table 3.3) is not very active, but in the presence of acid (entry 3) the activity is increased dramatically with excellent selectivity for O-allylation. The lifetime of this catalyst in the presence of acid, however, appears to be rather short, as after 30 minutes the conversion hardly increases. Catalyst stability was tested by adding a second batch of substrates **1** and **2** after three hours, and while all other catalysts converted this newly introduced batch in a similar manner as the

original batch, the [RuCp(*o*-MeOdppdmp)](OTs) did not show significant continued conversion. Degradation of the complex is thought to occur by cleavage of a methyl group from the anisyl ring, creating a strongly coordinating phenoxyl anion, for which there is precedence in literature.[12,13] The catalyst [RuCp(dppib)](OTs) (entry 4) in the presence of acid also shows a much higher activity, but the selectivity for O-allylation is decreased in a dramatic way and after three hours its performance is very similar to that of the non-substituted $[RuCp(dppp)]^+$ (entry 6). Finally, for the catalyst with the dimethylsilane-bridged ligand [RuCp(dpptms)](OTs) (entry 5) the activity and selectivity appear comparable to that of [RuCp(dppdep)](OTs).

3.2.5 Transallylations

In Chapter 2, it has been shown that allyl ethers can also be activated at the ruthenium center. The transallylation activity has been used as a diagnostic test to investigate the reactivity of the catalysts for the conversion of **3** in the presence of *p*-cresol. The results of this investigation using [RuCp(dppdmp)](OTs) as the catalyst are given in Table 3.5. Hardly any activity is observed in the absence of acid, but in the presence of acid the reaction reaches equilibrium within one hour, forming equal amounts of the allyl ethers of 4-*tert*-butylphenol and *p*-cresol. Only a small amount of C-allylated products is co-produced. These results thus indicate a strong co-catalytic role of protons in the oxidative addition of allyl phenyl ether, similar to that encountered in the activation of allyl alcohol. The results clearly show that trans-allylation of **3** with *p*-cresol proceeds with good selectivity when dppdmp is applied as the ligand. A considerably smaller loss to thermodynamically more favorable C-allylated products is observed compared to the catalyst with the ligand dppp (entry 3). This is consistent with the observations in the direct allylation of phenol with allyl alcohol (Table

Table 3.5. Transallylation of **3** with *p*-cresol in the presence of $[RuCp(dppdmp)]^+$ [a]



3 **1** + C-allylated products

entry	acid	conversion of **3** (%)	selectivity (%)[b]	
			O-allyl	**C-allyl**
1	-	~0	-	-
2	HOTs	64	86	14
3[c]	HOTs	80	55	45

[a] Reaction conditions: **3**/*p*-cresol/[RuCpCl(dppdmp)]/AgOTs/(HOTs) = 1000/1000/1/2/(2), 100 °C, toluene, 1 h
[b] O-allyl = total O-allylated products; C-allyl = total C-allylated products
[c] [RuCpCl(dppp)] was used; taken from Chapter 2

3.3) and confirms the tremendous effect of the ligand choice in the selectivity determining step in the catalytic cycle.

3.2.6 Kinetically stable chelate vs steric hindrance

Moloy and co-workers[14,15] have investigated the influence of substitution on the ligand backbone in reductive elimination reactions involving Pd and Pt complexes. Mul *et al.*[16] have reported a surprising effect of geminal dialkyl substitution of C_3-bridged diphosphine ligands in Pd-catalyzed olefin-carbon monoxide copolymerization. As shown above, the *geminal* dialkyl substitution of ligand backbones also has a positive influence on the system of (diphosphine)Ru-catalyzed allylation of phenol, apparently by blocking the C-allylation pathway. It has been proposed in Chapter 2 that restricted coordination space at the Ru center is a crucial catalyst parameter to prevent C-allylation. The question arises how the geminal dialkyl substitution at the central carbon of a C_3-backbone can influence the coordination space at ruthenium.

From the NMR and X-ray data of the catalyst precursor Ru(II) complexes it is concluded that the stereo-electronic coordination properties of the ligands do not change significantly upon backbone substitution; it is therefore reasonable to assume that the same is true for the proposed catalytic Ru(IV) intermediates shown in Scheme 3.1. Since the substituents at the central carbon atom are directed away from the reactive center, a significant contribution to the immediate static steric environment is not expected, both in the Ru(II) and the Ru(IV) complexes. Thus, it is very likely that the stability of the chelate under reaction conditions is the prime factor discriminating the substituted from the unsubstituted ligand. The Ru(II)Cp complexes with the *geminal* substituted ligands are highly stable, even in solutions of different solvents in air over longer periods of time, whereas complexes of the bidentate phosphine ligands with unsubstituted bridges (dppm, dppe and dppp) are oxidized within a few hours.

Therefore, it is concluded that that it is the kinetically stable chelation of these ligands which is the major cause for the high selectivity of their ruthenium complexes for O-allylation, i.e. an effect similar in origin as the "*gem*-dialkyl effect" coined by Moloy et al.[15] For diphosphine ligands with substituted backbones rotational freedom necessary for phosphine dissociation is severely limited; the equilibrium between the gauche- and anti-conformation (Figure 3.3), lies more towards the gauche-conformer where chelation takes place. Without substituents on the ligand backbone, the interactions are weak and rotation will be far less

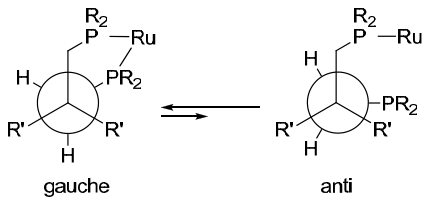


Figure 3.3. Schematic representation of the rotational restriction caused by *gem*-dialkyl substitution in a ruthenium diphosphine complex.

hindered. Introduction of additional substituents on the phenyl rings on the phosphorus atom as in [RuCp(*o*-MeOdppdmp)](OTs) will decrease the rotational freedom even further.[16] For a rigid ligand like dppib, which may be considered a special case of *gem*-disubstitution, rotational freedom is reduced due to the sp^2 hybridisation of the central carbon in the bridge. However, especially in the presence of acid, the catalyst with this ligand does not show a high selectivity towards O-allylation. It is proposed that the substitution causing rotational restriction and thereby selectivity for O-allylation decreases in the series dppdep > dppdmp > dppib > dppp.

The complex of the ligand with substitution pattern other than C_2-*geminal* dialkyl, the 1,3-substitution in 2,4-dpppt, also shows increased selectivity for O-allylation. A Newman projection cannot be used to explain loss of rotational freedom, but apparently for this complex also a more stable chelate is formed. However, in this case also the electronic environment on ruthenium is altered, making it impossible to point out the effect that is of highest importance for the higher selectivity.

3.2.7 Mechanistic implications

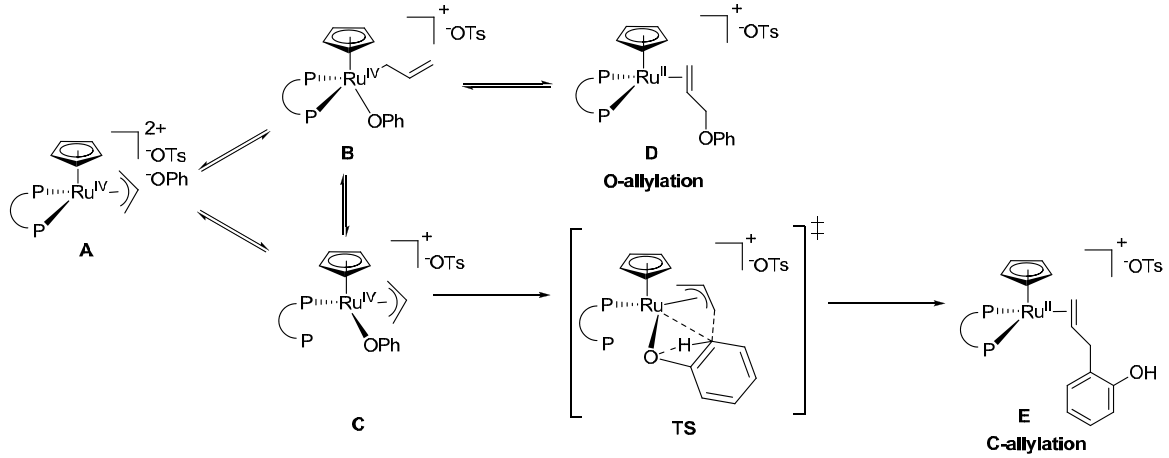
A catalytic cycle for the allylation of phenol with allyl alcohol catalyzed by ruthenium-Cp bidentate phosphine complexes has been proposed in Chapter 2. The oxidative addition of allyl alcohol in [Ru(II)Cp(PP)(allyl alcohol)](OTs) followed by exchange of the hydroxyl with a phenolate group will produce the resting state [Ru(IV)Cp(PP)(π-allyl)](OPh)(OTs) (**A**) (Scheme 3.2). The phenolate anion, however, will be strongly attracted to the Ru(IV) ion in the dicationic complex. In order to prevent the formation of a 20-electron species, either the σ-allyl intermediate (**B**) is formed or a phosphine donor must dissociate (**C**). The route via the σ-allyl species is the analogous microscopic reverse of the oxidative addition of allyl alcohol (or ether) and will produce the O-allylated product allyl phenyl ether (**D**). When phosphine dissociation occurs, space is provided for the activation of the *ortho*-position of the phenyl

ring possibly via the transition state **TS** (Scheme 3.2) and C-allylated products can then be irreversibly formed (**E**).

The previous finding that [RuCp(dppm)](OTs) and [RuCp(dppe)](OTs) demonstrate a high selectivity to C-allylated product can now thus be interpreted as probably not due to the ample free coordination space at Ru due to the relatively small static bite angle of these diphosphine ligands, but rather to the ease of dissociation of one phosphine donor under allylation reaction conditions.

Generally, the catalysts containing *gem*-dialkyl substituted ligands are considerably less active for allylation of phenol than their unsubstituted analogues. This is in particular true in the absence of protic co-catalyst. Clearly, the oxidative addition of allyl alcohol is the rate-determining step in the overall catalytic cycle. Oxidative addition requires the penetration of the allyl alcohol (or allyl ether) substrate into the coordination sphere of the Ru(II) complex. It is thought that a kinetically stable chelate cannot easily provide sufficient coordination space to fulfill this requirement. In the ideal case, for high activity one would like to use flexible chelates during the oxidative addition step, such that allyl alcohol can easily penetrate the Ru(II) coordination sphere. However, for high selectivity kinetically stable chelation at the intermediate Ru(IV) center is required as is discussed above. These requirements seem conflicting.

Although the binding properties of the C_2-*geminal* substituted C_3 ligands have been determined for the Ru(II) complexes and selectivity for O-allylation is controlled by a Ru(IV) species for which phosphines will have different binding strengths, it is concluded that the reduction of rotational freedom of the ligand must be the cause of the higher selectivity for O-allylation. Similarly, the high selectivity of [Ru(IV)Cp*(π-allyl)(acetonitrile)$_2$](PF_6)$_2$ catalyst



Scheme 3.2. Part of catalytic cycle for allylation with [RuCp(PP)](OTs) complexes where selectivity is determined.

precursors for C-allylation[7] is rationalized to the rapid dissociation of the weakly-coordinating acetonitrile ligand. This is in contrast with the reported mechanistic proposal that C-allylation of phenol proceeds via an external electrophilic attack of phenol by the Ru-π-allyl species, without pre-coordination of phenol at the Ru(IV) center.[7]

The results provide a firm confirmation that the *gem*-dialkyl effect can serve as a diagnostic tool to probe possible chelate-ring opening in a catalytic reaction pathway, which in this case discriminates C-allylation vs O-allylation routes.

3.3 Conclusions

In the present research, a class of bidentate phosphine ligands that form kinetically stable chelates on ruthenium has been investigated for their use in the catalytic allylation of phenol. It is shown that this type of ligands has a highly beneficial effect on the selectivity of the ruthenium catalysts for O-allylation; the thermodynamically favored C-allylation can be efficiently blocked even after long reaction times. The cause of the kinetically stable chelating properties of these ligands is due to a reduced rotational freedom of the ligands. Therefore entropy gain on dissociation is low, which causes the ligand to remain coordinated onto ruthenium thus inducing high selectivity towards O-allylation. The rigidity of the ligand is also expected to hinder oxidative addition of allyl donors at Ru(II), which is considered to be the rate-determining step, explaining the relatively lower activity of complexes with C_2-*geminal* substituted C_3-bridging ligands. The *gem*-dialkyl effect is thus used both as diagnostic tool for detecting chelate-ring opening at the metal center in a selectivity-determining step of the catalytic cycle, and at the same time as a means to develop catalysts for the allylation of phenol with allyl alcohol with the desired high O-allylation selectivity.

3.4 Experimental

General remarks. All reactions were performed under an argon atmosphere using standard Schlenk techniques. Solvents were dried and distilled by standard procedures and stored under argon. The phosphine ligand (S,S)-2,3-dppb was commercially available and used as received. A modified protocol for the synthesis of the phosphine ligands was used.[17] The ligands 2,2-dppp,[18] dppdmp,[19] dppdep,[20] dpptms,[21], 2,4-dpppt,[20] dppib,[22] and *o*-MeOdppdmp[23] were earlier described in literature. C, H determinations were performed on a Perkin Elmer 2400 Series II analyzer. ^{1}H NMR spectra (300 MHz), and ^{31}P{^{1}H}NMR spectra (121.4 MHz) were measured on a Bruker DPX-300. Chemical shifts are reported in ppm. Proton chemical shifts are relative to TMS, and phosphorus chemical shifts are relative to 85% aqueous H_3PO_4. The spectra were taken at room temperature.

General procedure for ligand synthesis. $HPPh_2$ (1.0 ml, 6 mmol) was dissolved in THF (5 ml) and cooled to 0 °C. Butyl lithium (3.75 ml of a 1.6 M solution in hexanes) was added and the mixture was stirred at room temperature for 1 h. The appropriate dibromo-bridge was added (3 mmol) and the resulting solution was stirred for 16 h at room temperature. Water was added (10 ml) and the organic solvent was evaporated. The product was extracted with 3 times 10 ml of CH_2Cl_2, after which the organic layers were collected and the solvent was removed *in vacuo*. The product was precipitated from the remaining oil by addition of methanol.

General procedure for RuCpCl(PP) synthesis. A solution of $RuCpCl(PPh_3)_2$ (72 mg, 0.1 mmol) and the bidentate phosphine ligand (0.1 mmol) in 5 ml toluene was stirred for 16 h at 90 °C. The solution was cooled to room temperature and flushed over a column of silica gel (3 g, d = 1 cm) with 15 ml of toluene to remove triphenylphosphine. Finally, the orange product was eluted with ethyl acetate until the eluate was colorless. The solution was then concentrated in *vacuo* to approximately 1 ml and the product precipitated with petroleum ether.

[RuCpCl(dppdmp)] was obtained as a yellow solid in a yield of 54 mg (84%). Crystals suitable for X-ray diffraction were obtained by slow diffusion of n-hexane into a solution of the complex in toluene. Anal. Calcd for $C_{34}H_{35}ClP_2Ru \cdot 0.33$(toluene): C, 64.86; H, 5.64. Found: C, 64.64; H, 6.13. ^{1}H-NMR ($CDCl_3$): δ 7.63-7.49 (m, 8H, ArH), 7.35-7.26 (m, 12H, ArH), 4.48 (s, 5H, Cp), 3.02-2.95 (m, 2H, PCH), 2.17-2.10 (m, 2H, PCH), 1.02 (s, 3H, Me), 0.18 (s, 3H, Me). ^{31}P{^{1}H}-NMR ($CDCl_3$): δ 40.0 (s).
[RuCpCl(dppdep)] was obtained as a yellow solid in a yield of 53 mg (79%). Crystals suitable for X-ray diffraction were obtained by slow diffusion of n-hexane into a solution of the complex in toluene. Anal. Calcd for $C_{36}H_{39}ClP_2Ru \cdot 0.25$(hexane)$\cdot 0.25$(water): C, 65.05; H, 6.28. Found: C, 64.61; H, 6.34. ^{1}H-NMR ($CDCl_3$): δ 7.67-7.61 (m, 4H, ArH), 7.51-7.45 (m, 4H, ArH), 7.37-7.30 (m, 12H, ArH), 4.39 (s, 5H, Cp), 2.87-2.79 (m, 2H, CH_2P), 2.18-2.09 (m, 2H, CH_2P), 1.25 (q, 2H, *J* = 7 Hz, CH_2), 0.71 (q, 2H, *J* = 7 Hz, CH_2), 0.64 (t, 3H, *J* = 7 Hz, CH_3), 0.14 (t, 3H, *J* = 7 Hz, CH_3). ^{31}P{^{1}H}-NMR ($CDCl_3$): δ 39.6 (s).
[RuCpCl(*o*-MeOdppdmp)] was obtained as a yellow solid in a yield of 64 mg (84%). Crystals suitable for X-ray diffraction were obtained by slow diffusion of n-hexane into a solution of the complex in toluene. Anal. Calcd for $C_{38}H_{43}ClO_4P_2Ru \cdot 1.5$(toluene): C, 62.21; H, 5.91. Found: C, 62.20; H, 6.16. ^{1}H-NMR ($CDCl_3$): δ 7.37-7.12 (m, 8H, ArH), 7.03-6.93 (m, 7H, ArH), 6.69 (d, 4H, *J* = 8 Hz, ArH), 4.42 (s, 5H, Cp), 3.29 (s, 6H, OMe), 3.24 (s, 6H, OMe), 2.91-2.89 (m, 2H, CH_2), 2.62-2.60 (m, 2H, CH_2), 0.88 (s, 3H, Me), 0.25 (s, 3H, Me). ^{31}P{^{1}H}-NMR (acetone-d_6): δ 38.1 (s).
[RuCpCl(dpptms)] was obtained as a yellow solid in a yield of 52 mg (81%). Crystals suitable for X-ray diffraction were obtained by slow diffusion of n-hexane into a solution of the complex in toluene. Anal. Calcd for $C_{33}H_{35}ClP_2Ru \cdot 1.25$(water): C, 60.73; H, 5.79. Found: C, 60.35; H, 5.84. ^{1}H-NMR ($CDCl_3$): δ 7.70-7.64 (m, 4H, ArH), 7.37-7.25 (m, 16H, ArH), 4.21 (s, 5H, Cp), 2.33-2.26 (m, 2H, PCH), 1.54-1.44 (m, 2H, PCH), -0.03 (s, 3H, Me), -0.38 (s, 3H, Me). ^{31}P{^{1}H}-NMR ($CDCl_3$): δ 42.0 (s).
[RuCpCl(2,4-dpppt)] was obtained as a yellow solid in a yield of 70 mg (90%). Anal. Calcd for $C_{34}H_{35}ClP_2Ru \cdot 0.25$(hexane): C, 64.25; H, 5.85. Found: C, 64.23; H, 6.14. ^{1}H-NMR ($CDCl_3$): δ 7.85-7.82 (m, 4H, ArH), 7.37-7.34 (m, 8H, ArH), 7.27-7.20 (m, 8H, ArH), 4.13 (s, 5H, Cp), 3.23-3.16 (m, 2H, PCH), 2.03-1.81 (m, 2H, CH_2), 1.13 (bs, 6H, CH_3). ^{31}P{^{1}H}-NMR ($CDCl_3$): δ 51.8 (s).

[RuCpCl(dppib)] was obtained as a yellow solid in a yield of 40 mg (92%). Anal. Calcd for $C_{33}H_{31}ClP_2Ru \cdot 0.33$(hexane): C, 64.20; H, 5.49. Found: C, 63.78; H, 5.87. ^{1}H-NMR ($CDCl_3$): δ 7.76-7.71 (m, 4H, ArH), 7.36-7.35 (m, 8H, ArH), 7.26-7.10 (m, 8H, ArH), 4.68 (s, 2H, $=CH_2$), 4.42 (s, 5H, Cp), 3.68-3.59 (m, 2H, CH_2P), 3.22-3.12 (m, 2H, CH_2P). $^{31}P\{^1H\}$-NMR ($CDCl_3$): δ 43.0 (s).

[RuCpCl(2,2-dppp)] was obtained as a yellow / orange solid in a yield of 61 mg (99%). Crystals suitable for X-ray diffraction were obtained by slow diffusion of n-hexane into a solution of the complex in toluene. Anal. Calcd for $C_{32}H_{31}ClP_2Ru \cdot 0.5$(toluene) ·(water): C, 62.88; H, 5.50. Found: C, 62.88; H, 5.98. ^{1}H-NMR ($CDCl_3$): δ 7.95-7.89 (m, 4H, ArH), 7.50-7.33 (m, 16H, ArH), 4.52 (s, 5H, Cp), 1.73 (t, 3H, J = 13 Hz, CH_3), 1.26 (t, 3H, J = 13 Hz, CH_3). $^{31}P\{^1H\}$-NMR ($CDCl_3$): δ 43.0 (s).

[RuCpCl({S,S}-2,3-dppb)] was obtained as a yellow solid in a yield of 60 mg (96%). Anal. Calcd for $C_{32}H_{31}ClP_2Ru \cdot 0.3$(toluene)·0.3(hexane): C, 65.22; H, 5.91. Found: C, 64.96; H, 6.18. ^{1}H-NMR ($CDCl_3$): δ 7.91-7.87 (m, 2H, ArH), 7.64-7.41 (m, 9H, ArH), 7.31-7.23 (m, 4H, ArH), 7.11-7.05 (m, 2H, ArH), 4.30 (s, 5H, Cp), 2.68-2.62 (m, 1H, CH), 2.07-2.03 (m, 1H, CH), 1.01 (dd, 3H, J = 7 Hz, J = 11 Hz, CH_3), 0.80 (dd, 3H, J = 7 Hz, J = 11 Hz, CH_3). $^{31}P\{^1H\}$-NMR ($CDCl_3$): δ 86.0 (d, J = 41 Hz), 64.5 (d, J = 41 Hz).

Table 3.6. Crystal data and structure refinement for the complexes [RuCpCl(dppdep)], [RuCpCl(dppdmp)], [RuCpCl(dpptms)], [RuCpCl(o-MeOdppdmp)] and [RuCpCl(2,2-dppp)]

	[RuCpCl (dppdep)]	[RuCpCl (dppdmp)]	[RuCpCl (dpptms)]	[RuCpCl(*o*-MeOdppdmp)]	[RuCpCl (2,2-dppp)]
formula	$C_{36}H_{39}ClP_2Ru \cdot \frac{1}{2}(C_7H_8)$	$C_{34}H_{35}ClP_2Ru$	$C_{33}H_{35}ClP_2RuSi$	$C_{38}H_{43}ClO_4P_2Ru$	$C_{32}H_{31}ClP_2Ru$ + unresolved solvent molecules
fw	716.20	642.08	658.16	762.18	614.03*
crystal form	yellow plate	orange plate	orange block	orange thick plate	orange plate
crystal size [mm^3]	0.35 × 0.17 × 0.06	0.35 × 0.21 × 0.06	0.30 × 0.25 × 0.23	0.23 × 0.18 × 0.07	0.37 × 0.20 × 0.10
crystal system	monoclinic	monoclinic	monoclinic	monoclinic	triclinic
space group	$P2_1/c$ (no. 14)	$P2_1/c$ (no. 14)	$P2_1/c$ (no. 14)	$P2_1/c$ (no. 14)	$P2_1/c$ (no. 14)
a [Å]	15.2270(6)	13.3991(9)	9.4136(4)	10.7944(3)	19.5137(1)
b [Å]	14.1527(8)	10.8631(7)	17.9105(7)	17.0749(2)	11.2169(3)
c [Å]	18.0689(7) Å	19.9844(9)	18.2181(9)	38.2828(4)	30.1980(15)
α [°]	-	-	-	-	-
β [°]	119.047(3)	96.917(2)	103.927(2)	96.808(1)	119.551(3)°
γ [Å^3]	-	-	-	-	-
V [Å^3]	3404.1(3)	2887.7(3)	2981.3(3)	7006.3(2)	5750.0(4)
Z	4	4	4	8	8
D_x [g/cm^3]	1.40	1.48	1.47	1.45	1.42*
μ [mm^{-1}]	0.66	0.77	0.79	0.65	0.77*
abs. corr. method					
abs. corr. range	0.77–0.96	0.70–0.95	0.76–0.84	-	0.73–0.93
refl. (meas./unique)	42872/7807	47036/6637	41351/6839	100289/12389	67490/13221
param./restraints	427 /171	345/0	345/0	842/0	731/256
R1/wR2 [I>2σ(I)]	0.0248/0.0514	0.0217/0.0511	0.0175/0.0420	0.0424/0.0863	0.0324/0.0711
R1/wR2 [all refl.]	0.0362/0.0551	0.0263/0.0532	0.0207/0.0436	0.0588/0.0931	0.0490/0.0761
S	1.022	1.052	1.098	1.081	1.048
$\rho_{min/max}$ [e/Å^3]	–0.44 - 0.42	–0.49 - 0.90	–0.30 - 0.35	–0.64 - 2.2	–0.52 - 0.52

[*]excluding the unresolved entity contribution

General procedure for catalytic reactions. 5 mmol of 4-*tert*-butylphenol (or in some experiments 4-*tert*-butylphenyl allyl ether), 0.005 mmol of the ruthenium complex, 0.01 mmol of AgOTs and, if indicated, 0.01 mmol of additive were charged into the reaction vessel and flushed with argon. Degassed and dried toluene was added (5 ml) and the mixture was stirred for five minutes. Allyl alcohol (or in some experiments *p*-cresol) was added (5-10 mmol) and the reaction was stirred at 100 °C. Samples were taken at certain time intervals with an airtight syringe and analyzed by gas chromatography (Chapter 2).

GLC method. Quantitative gas liquid chromatography analyses were carried out on a Varian CP-3800 apparatus equipped with a VF-1ms (25 m × 0.25 mm) column with decane as internal standard. The temperature gradient used was: isothermal for 5 minutes at 40 °C, heating 10 °C/ minute to 250 °C and finally isothermal for 5 minutes at 250 °C.

X-ray crystallography. All reflection intensities were measured at 150(2) K using a Nonius KappaCCD diffractometer (sealed tube for compounds **a**, **b**, **c** and **d**, or rotating anode for compounds **e**, **f**, and **g**) with graphite-monochromated Mo $K\alpha$ radiation (λ = 0.71073 Å) under the program COLLECT.[24] The programs PEAKREF[25] or HKL2000[26] were used to refine cell dimensions. Data were reduced using the integration programs EvalCCD[27] or HKL2000.[26] All structures were solved with DIRDIF99[28] or SHELXS-97 and were refined on F^2 with SHELXL-97.[29] Multi-scan semi-empirical absorption corrections based on symmetry-related measurements were applied to all data (except for [RuCpCl(*o*-MeOdppdmp)]) using SADABS (Version 2006/1)[30] or TWINABS Version 1.05.[31] The data collection temperature was controlled using the system Oxford Cryostream 600 (manufactured by Oxford Cryosystems). The H-atoms (except when specified) were placed at calculated positions (instructions AFIX 23, 43 or 137) with isotropic displacement parameters having values 1.2 or 1.5 times U_{eq} of the attached C atoms, and were refined with a riding model. Geometry calculations, structure validations and illustrations were made with the PLATON program.[32] For [RuCpCl(*o*-MeOdppdmp)]: The crystal that was mounted on the diffractometer was not single but rather an aggregate of two single crystals stuck in an arbitrary arrangement. The program DIRAX[33] found the two orientations matrices. The fractional contribution of the minor component (*i.e.*, the BASF batch scale factor) refined to 0.1520(10). For [RuCpCl(2,2-dppp)]: SQUEEZE details: two voids of 152 Å^3 filled with 32 electrons (all numbers are given per unit cell). Relevant crystal structure and refinement data are provided in Table 3.6.

3.5 References

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4

Remarkable activity of the isomerization catalyst $[RuCp(PPh_3)_2](OTs)$ in O-allylation of phenol with allyl alcohol

Abstract
It was surprisingly found that the highly active allyl alcohol redox isomerization catalyst $[RuCp(PPh_3)_2](OTs)$ upon addition of a catalytic amount of a strong acid can change its catalytic action fully to the selective O-allylation of phenols with allyl alcohol. High turnover numbers (75,000 based on phenol; 200,000 based on allyl alcohol) are reached and the catalyst is very stable in the presence of substrate. Addition of triphenylphosphine to the reaction mixture does not lead to further stabilization of the catalyst; instead the free phosphine is rapidly allylated, thereby consuming the acid, which deactivates the catalytic system for allylation reactions. This catalyst with monodentate phosphine ligands is superior in both activity and selectivity to similar catalysts with bidentate phosphine ligands. Apart from phenols, also thiophenol can be efficiently allylated to form allyl phenyl sulfide.

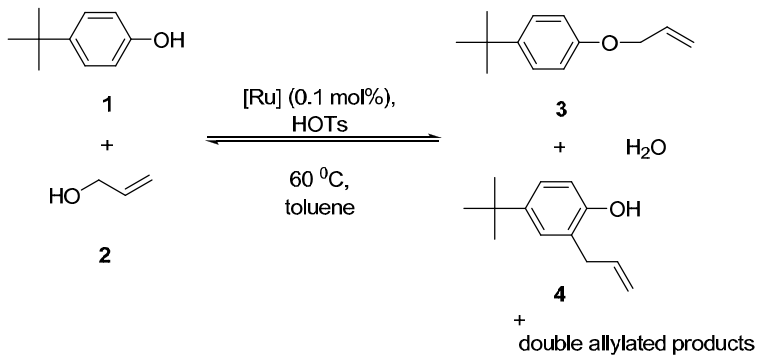
This Chapter is based on: J.A. van Rijn, E. van Stapele, E. Bouwman, E.Drent, J. Catal. 2010, 272, 220-226.

4.1 Introduction

The development of an environmentally benign catalytic route to epoxy resins is highly desirable.[1,2] The bis O-allylation of bisphenol A, is regarded as an interesting intermediate pathway in the production of these epoxy resins, in particular, if catalysts could be developed for the catalytic O-allylation reaction. It would, of course be best if allyl alcohol could be used as the allylating agent in view of the protection of the environment, since only water would be co-produced in ether formation. Prior to the work described in this thesis, only a single example was known where allyl phenyl ethers can be catalytically and selectively produced from a phenol and allyl alcohol;[3] however, a stoichiometric amount of base needs to be added to induce O-allylation of phenols. This addition of base should be avoided, because stoichiometric amounts of saline waste will be co-produced. However in the absence of such a base, similar systems based on ruthenium[4] or palladium[5] exclusively yield C-allylated phenolic products.

In Chapter 2, the development of ruthenium-based catalytic systems has been reported that catalyze both O- and C-allylation of phenols (Scheme 4.1), without the need of any stoichiometric amount of additives. It has been shown that the O-allylated products are reversibly formed, while C-allylated products are produced irreversibly. Restricted coordination space at the ruthenium center favors the formation of the O-allylated product, which could be achieved by using ligands that have a large bite angle and/or form kinetically stable chelates (Chapter 3). It was also observed that [RuCp(dppb)](OTs), a catalyst known to be active in the isomerization of allyl alcohol into propanal,[6] becomes moderately active in allylation reactions in the presence of. 2 equivalents on Ru of a strong acid.

The cationic ruthenium complex, based on a monodentate ligand, triphenylphosphine, i.e. $[RuCp(PPh_3)_2]^+$, has been reported to be an extremely active and efficient catalyst for the



Scheme 4.1. Reaction of 4-tert-butylphenol (**1**) with allyl alcohol (**2**) catalyzed by different $[RuCp(PP)]^+$ complexes.

redox isomerization of allyl alcohols into carbonyl compounds, achieving very high turnover numbers. The catalyst is applicable for a wide range of allylic substrates.[7-9] Similar ruthenium complexes with chelating phosphine ligands proved to be much less active in the isomerization reaction,[6] but switch reactivity to allyl ether formation in the presence of isoprene. Surprisingly, it has been found that the isomerization catalyst [RuCp(PPh$_3$)$_2$]$^+$ can be transformed into an extremely active and selective catalyst for allyl phenyl ether formation from a phenol and allyl alcohol.

4.2 Results and discussion

4.2.1 Acid effect

In Chapter 2 it has been shown that the catalytic allyl ether formation is enhanced by addition of two equivalents of acid on ruthenium. However, under those conditions (at 100 °C) the use of [RuCp(PPh$_3$)$_2$](OTs) results in only low conversion of phenol, and propanal is still produced as the major product. It was found that at lower reaction temperatures and higher acid concentrations the production of propanal can be effectively prevented and the catalyst becomes extremely active and selective in the O-allylation of phenols (Table 4.1).

As expected, in the absence of acid no reactivity for allylation is observed (entry 1). Gradually increasing the acid concentration results in higher yields of the desired allyl ether, but still propanal is the major product (entries 2-4). In a reaction mixture with 20 mM of HOTs (2 mol% on phenol) the production of propanal is completely blocked and a high conversion of **1** is achieved. The selectivity for O-allyl ether **3** is very high for this acid concentration and the catalyst remains selective also after longer reaction times (6 h). When the concentration of HOTs is increased beyond 20 mM, the selectivity drops significantly, with only marginal increase in the conversion of **1**. Therefore, 20 mM HOTs at 60 °C was used in the further experiments. Without the ruthenium complex but with the acid only, no allylation or allyl alcohol isomerization is observed, thus clearly providing evidence for ruthenium complex catalyzed reactions that can be tuned by the acid.

It has also to be noted that dehydrative condensation of allyl alcohol to give diallyl ether tends to precede the allylation of the phenol. Thus, diallyl ether mainly functions as the actual phenol allylation agent and it has been shown that diallyl ether performs as an equally suitable allylation agent as allyl alcohol. As half the water is being co-produced overall, diallyl ether would in fact be the allylation agent of choice in commercial applications, allowing high phenol conversion, in particular at high diallylether/phenol substrate ratios.

Table 4.1. Conversion of 1 and selectivity for **3** using [RuCp(PPh_3)$_2$](OTs) as catalyst at 60 °C with the addition of different amounts of HOTs.[a]

entry	mM HOTs	conversion of **1** (%) 1 h	conversion of **1** (%) 6 h	selectivity for **3** (%)b 6 h	yield of propanal (%)[c] 6 h
1	0	0	0	-	100
2	1	6	7	100	79
3	2	8	9	100	62
4	4	28	31	100	38
5	10	32	39	95	11
6	20	40	70	86	0
7	50	43	75	86	0
8	100	45	74	58	0
9	200	26	69	40	0

[a] Reaction conditions: Ratio **1/2**/[RuCpCl(PPh_3)$_2$]/AgOTs = 1000/2000/1/2; toluene; 60 °C. 1 mM [RuCpCl(PPh_3)$_2$].
[b] based on **1** converted
[c] based on **2**

Under these conditions, high turnover numbers could be obtained by decreasing the Ru catalyst concentration (to 0.05 mM) and as many as 14300 turnovers were achieved in a single batch experiment (after 24 hours, 72% conversion of **1** with 87% selectivity for O-allylation), demonstrating the stability of the catalyst (Figure 4.1). After a small induction time caused by relatively slow formation of [RuCp(PPh_3)$_2$](OTs) from [RuCp(PPh_3)$_2$Cl] and AgOTs in the diluted reaction medium, a linear increase in turnover number vs time is observed. After about 24 hours (72% conversion of **1**) the conversion is halted.

In order to see if even higher turnover numbers can be achieved, a similar reaction was performed, but with a phenol over catalyst ratio of 200,000. When this reaction was left for longer time (72 hours) a turnover of 75,000 is reached, based on **1**. In this time all the allyl

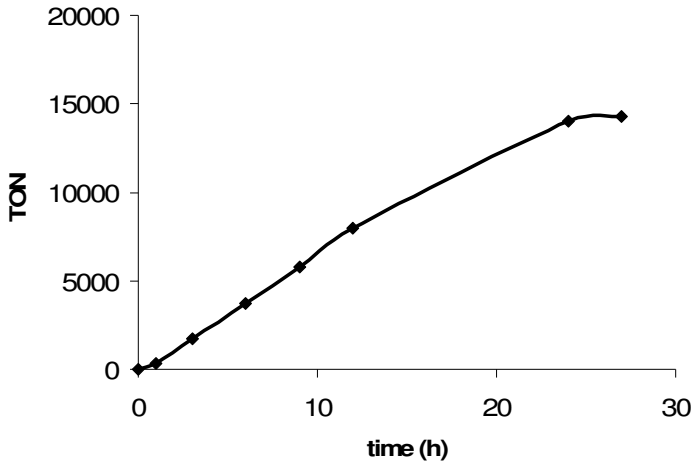


Figure 4.1 Total turnover number (TON) of phenol to allylated products in time (maximum TON = 20000) Reaction conditions: Ratio 4-*tert*-butylphenol/allyl alcohol/[RuCpCl(PPh_3)$_2$]/AgOTs/HOTs = 20000/40000/1/2/400; toluene; 60 °C.

alcohol is converted to either diallyl ether or allyl phenyl ether, the TON based on allyl alcohol is even higher than 200,000.

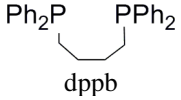
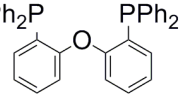
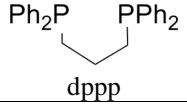
The allyl phenyl ether formation is an equilibrium condensation reaction and the substrate conversions at thermodynamic equilibrium will be determined by the amount of water that is soluble in the reaction medium (mainly toluene) at reaction temperature. *In situ* removing water from the reaction medium, for instance by means of a Dean-Stark trap, could lead to increased substrate conversion. A Dean-Stark water trap, however is not efficient at the reaction temperature used in these experiments. On the other hand, at the low reaction temperature applied of 60 °C, the solubility of water in the reaction medium is very low and the water produced forms a separate phase, thus shifting the dehydrative equilibrium in the toluene phase automatically towards high substrate conversion.

4.2.2 Monodentate phosphine vs bidentate phosphine ligands

The [RuCp(PPh$_3$)$_2$](OTs) catalyst was compared to catalysts containing bidentate ligands under the optimal conditions. The results are shown in Table 4.2.

Compared to any of the catalysts with a bidentate ligand (entries 2-4), the activity of [RuCp(PPh$_3$)$_2$](OTs) is very high (entry 1). Its selectivity is only slightly lower than that of the complexes with large bite angle bidentate ligands (entry 2-3). [RuCp(dppp)](OTs), with the smallest bite-angle ligand in this table, shows very low selectivity for O-allylation under the acidic conditions applied (entry 4).

Table 4.2. Conversion of **1** and selectivity for **3** for the allylation of 4-*tert*-butylphenol using different [RuCp(PP)]$^+$ complexes as catalysts.[a]

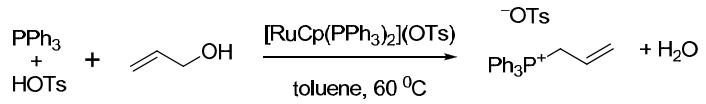
entry	PP	conversion of **1** (%)		selectivity for **3** (%)	
		1 h	6 h	1 h	6 h
1	2 PPh_3	40	70	93	86
2	 dppb	7	52	100	100
3	 dpppe	<1	42	100	100
4	 dppp	1	32	100	25

[a] Reaction conditions: Ratio **1**/**2**/[RuCpCl(PP)]/AgOTs/HOTs = 1000/2000/1/2/20; toluene; 60 °C.

Table 4.3. Rate constants for conversion of **1** with different amounts of added PPh_3.[a]

entry	added PPh_3 (eq on [Ru]) [b]	time (min)	conversion of **1** (%)	rate constant k (h^{-1})[c]
1	0	15	21	0.94
2	2	15	25	1.15
3	5	15	24	1.09
4	10	15	24	1.09

[a] Reaction conditions: Ratio 4-*tert*-butylphenol/allyl alcohol/[$RuCpCl(PPh_3)_2$]/AgOTs/HOTs = 1000/2000/1/2/20; toluene; 60 °C.
[b] after addition of 20 equivalents of PPh_3 or more the catalyst shows no activity for allylation, only propanal is formed quantitatively
[c] $k = -\ln\{1 - \text{conversion}(\%)/100]/t\}$ for t = 15 minutes.



Scheme 4.2. Formation of allyl phosphonium salt with stoichiometric consumption of acid and phosphine.

4.2.3 Reactivity of triphenylphosphine

The mechanism for the isomerization of allyl alcohols into carbonyl compounds requires that a phosphine ligand dissociates from the Ru(II) complex and this readily can occur in [$RuCp(PPh_3)_2$](OTs).[7] However, it appears that in the presence of a catalytic amount of acid, the allyl alcohol isomerization reaction is efficiently blocked. It is surmised that phosphine dissociation can still play a role in the catalytic allylation cycle and the stability of the catalyst. For this reason, triphenylphosphine was added in different amounts (2, 5, 10 and 20 eq on [Ru]) to the reaction mixture to test its effect on the stability and life time of the catalyst (Table 4.3).

The initial catalytic allylation rate of the catalyst after 15 minutes is not affected when 2 (entry 2) or 5 eq (entry 3) of PPh_3 is added compared to the rate of the reaction in the absence of PPh_3 (entry 1). Upon addition of 10 eq of PPh_3 the initial rate of allylation is unchanged (entry 4), but after 30 minutes, conversion of **1** is halted at 40% and a large amount of propanal is formed. Addition of 20 eq of triphenylphosphine or more completely inhibits the catalytic activity for allylation and only propanal is formed. The fate of free triphenylphosphine under reaction conditions was investigated and it was found that the reaction shown in Scheme 4.2 takes place: allyl alcohol reacts with triphenylphosphine and the acid under the agency of the catalyst, to form an allyl phosphonium salt and water. In the absence of catalyst, this quaternisation is not observed. A similar reaction has been reported by Basset *et al*. for a palladium complex.[10] The formation of propanal, when 20 equivalents of PPh_3 are added to the reaction, can thus be explained by the fact that the acid is consumed

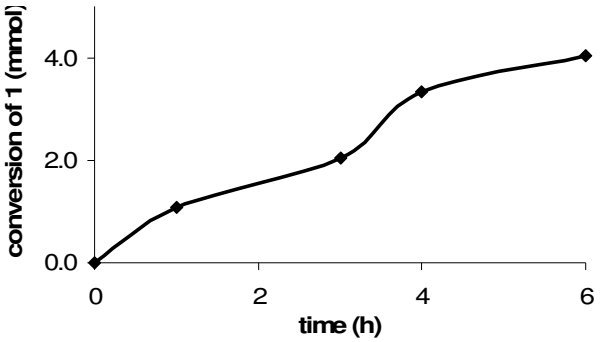


Figure 4.2. Conversion of **1** (4-tert-butylphenol) in time in the allylation reaction using allyl alcohol as the allylating agent. A second batch of the substrates was added after 3 hours.
Reaction conditions: Ratio 4-*tert*-butylphenol/allyl alcohol /[RuCpCl(PPh$_3$)$_2$] /AgOTs/HOTs = 1000/2000/1/2/20; toluene; 60 °C. 2.5 mmol 4-*tert*-butylphenol/5 mmol allyl alcohol per batch.

Table 4.4. Rate constants for first and second batch of 4-*tert*-butylphenol and allyl alcohol.[a]

entry	time (h)	conversion of **1** (mmol)	rate constant k (h^{-1})[b,c]
1	1	1.0	0.51
2	4	3.3[d]	0.73

[a] Reaction conditions: Ratio 4-*tert*-butylphenol/allyl alcohol /[RuCpCl(PPh$_3$)$_2$]/AgOTs/HOTs = 1000/2000/1/2/20; toluene; 60 °C. 2.5 mmol 4-*tert*-butylphenol per batch
[b] k= –ln{1 – conversion(%)/100]/t} for t= 1 h.
[c] k= –ln{1 – conversion(%)/100]/t} for t= 4 h (1 h after addition of second batch)
[d] cumulative conversion

quantitatively by the additional PPh$_3$. It is intriguing to see that whereas free triphenylphosphine is rapidly converted to an allyl phosphonium salt, even in the presence of a large excess of phenol, the two equivalents of coordinated triphenylphosphine are apparently not, since the catalyst remains stable for many hours and yielding high TON´s.

When, however a second batch of substrates is added to the catalyst after 23 hours (at 84% conversion of **1**), no further conversion is observed, but when this second batch of substrates is added after three hours, continued conversion proceeds smoothly, even without a reduction of the reaction rate (Figure 4.2; Table 4.4). In Figure 4.2 it is shown that the second batch of substrate, added after 3 hours reaction time, is converted with a similar rate as the initial batch. The quantitative data are reported in Table 4; the rate constant determined after one hour reaction time after the addition of the second batch (entry 2) seems to be even slightly higher than that of the initial batch (entry 1). However, reaction conditions at the start of the reaction and after three hours will not be exactly the same. Importantly, these data do indicate that in these three hours reaction time the catalyst is not significantly degraded. Apparently, the catalyst is stable at a high substrate over catalyst ratio as also observed from the high TON in the experiment with a very low catalyst concentration. However, when the reaction is near completion at relatively low substrate to catalyst ratio the catalyst deactivates. This

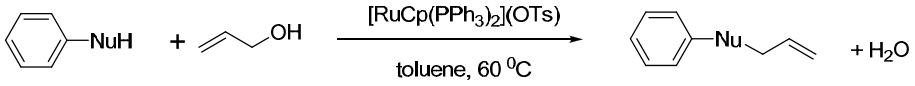
deactivation is accompanied with a color change of the reaction mixture from light yellow to brown.

4.2.4 Scope of the allylation reaction

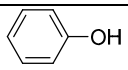
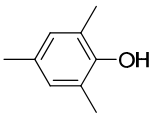
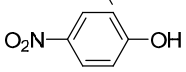
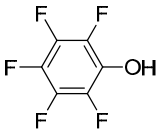
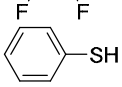
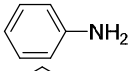
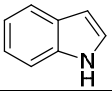
In order to explore the scope of the reaction, several other phenols were reacted with allyl alcohol (Table 4.5). Phenol itself also shows high reactivity towards allyl alcohol in the presence of the catalytic system (entry 1), with very high selectivity for the O-allylated product. The reaction with 2,4,6-trimethylphenol is logically completely selective towards O-allylation, but considerably slower (entry 2). Highly acidic phenols like *p*-nitrophenol (pKa = 7.08; entry 3) or pentafluorophenol (pKa = 5.49; entry 4) are not reactive for allylation. The increased acidity does not deactivate the catalyst, since diallyl ether formation is observed in both cases and therefore the decreased reactivity for O-allylation is attributed to the low nucleophilicity of the corresponding phenolates.

Nucleophilic substrates with other donor atoms than oxygen also proved to be reactive

Table 4.5. Conversion of **5** and selectivity for **6** for the allylation of several nucleophilic substrates with allyl alcohol.[a]



5 **2** **6**

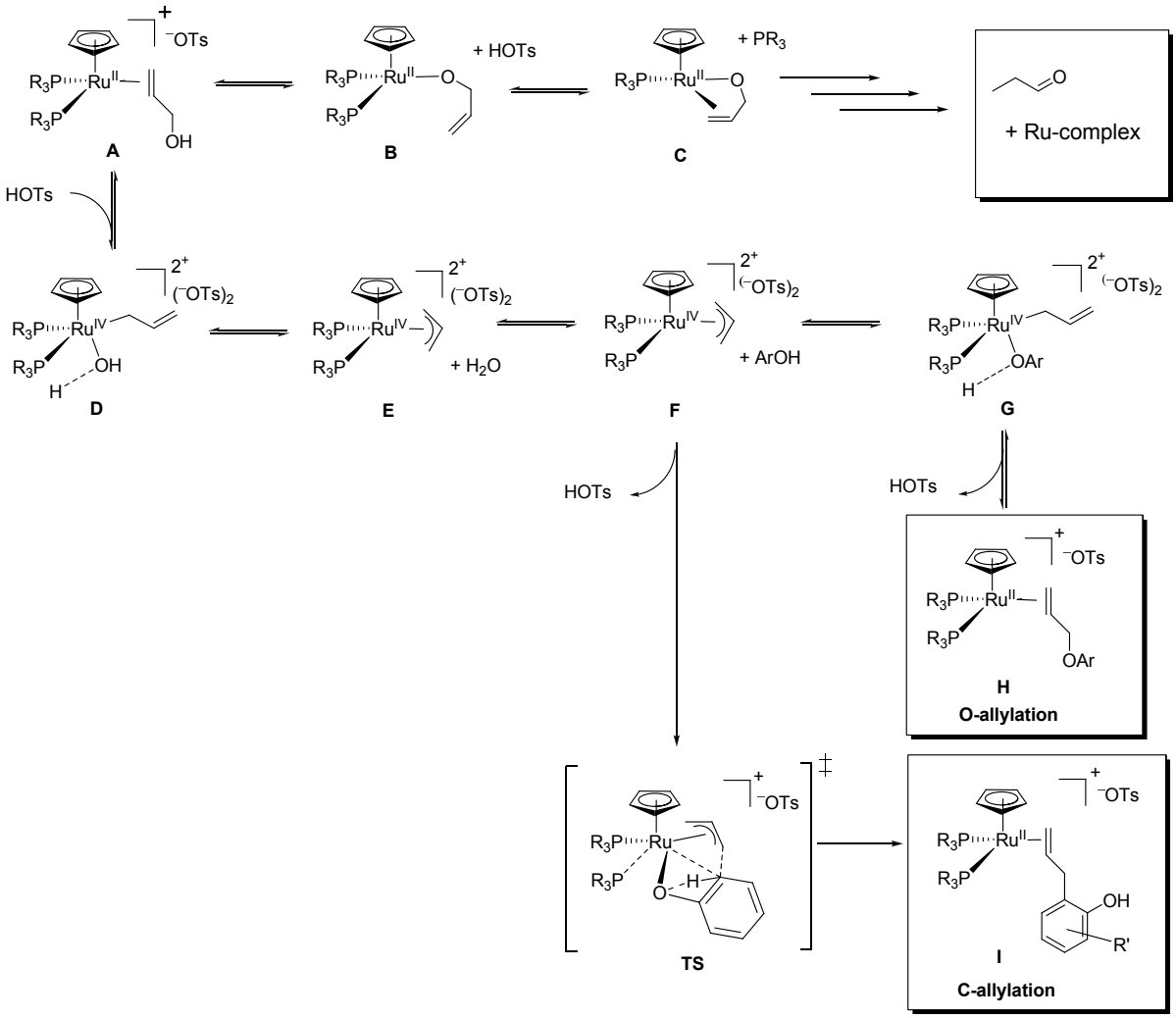
entry	**5** =	conversion after 3 h (%)	selectivity for **6** (%)
1		71	99
2		8	100
3		0[b]	-
4		0[b]	-
5		94	100
6		0	-
7		0[c]	-

[a] Reaction conditions: Ratio **5**/allyl alcohol/[RuCpCl(PPh$_3$)$_2$]/AgOTs/HOTs = 1000/2000/1/2/20; toluene; 60 °C, 3 h
[b] diallyl ether is formed
[c] propanal is formed

towards allylation. Thiophenol (entry 5) is efficiently S-allylated with complete selectivity towards the allyl phenyl sulfide. Aniline, however does not show any reactivity for allylation, and even diallyl ether formation (entry 6) does not take place in this instance. Apparently, aniline's N-coordination to Ru inhibits the catalyst completely. When a non-nucleophilic N-containing substrate like indole is used (entry 7), allylation is not observed, but propanal is quantitatively formed. This indicates the neutralization of acid by the indole functionality.
Substituted higher allyl alcohols can also be used as allylating agent, however these are considerably less reactive and the subsequent cross-allylation with phenols proceeds with lower selectivity for O-allylation. Due to the complicated product development with such alllylic alcohols, their reactions will be discussed in the next chapter.

4.2.5 Mechanistic implications

The mechanistic implications of the findings are summarized in Scheme 4.3. Allyl alcohol can coordinate to Ru(II) either with its olefin moiety (**A**) or via its alcoholate functionality (**B**).[9] Even in the absence of added protons, the alcoholate coordination mode is present only in very small amounts since this species escapes observation with NMR spectroscopy at room temperature. For isomerization towards the aldehyde to occur, it has been proposed that a phosphine ligand dissociates with consecutive coordination of the olefin moiety, forming species **C**.[9] After subsequent β-hydrogen elimination, a Ru(II)(enone)-hydride forms which after reinsertion of the enone moiety into Ru(II)-H gives a Ru(II)-oxa-allyl species. Protonation then results in the formation of the aldehyde.[9]
Addition of protons will affect the catalytic performance of the Ru complexes two-fold. First, added protons in mM quantities will dramatically suppress formation of the alcoholate species **B** by orders of magnitude due to a strong shift to the left of the alcoholate forming equilibrium (**A** ⇆ **B** + HOTs). This will thus strongly inhibit the catalytic isomerization pathway.



Scheme 4.3. Catalytic intermediates for isomerization of allyl alcohol into propanal (**A-C**; absence of acid; reference [6]) and O- and C-allylation with allyl alcohol as allylating agent (**A**, **D-I**; in the presence of acid).

Secondly, whereas the concentration of the major species in solution olefin-bound allyl alcohol (**A**) is not expected to be influenced by protons, a possible subsequent oxidative addition onto Ru(II) of the C-O bond in allyl alcohol will be strongly enhanced by protons, similar to that observed with other RuCp(PP)-cationic complexes, reported in Chapter 2 and 3. The significantly lower barrier for oxidative addition of species **A** caused by acid is rationalized by protonation of the OH moiety, thus transforming the poor hydroxyl leaving group into water as a good leaving group. This results initially in σ-allyl species **D** which subsequently rearranges to π-allyl intermediate **E.** As oxidative addition is thought to be rate-determining for allylation one can thus rationalize that added protons dramatically increase the rate of allylation at the cost of allyl alcohol isomerization.

After exchange of water with a phenol to form species **F**, either the microscopic analogous reverse reaction of (acid promoted) oxidative addition, i.e. reductive elimination of the allyl

ether takes place via a species **G**, eventually forming allyl ether bound species **H,** or, alternatively C-allylation of the phenol occurs, forming eventually Ru-bound C-allylated phenol product **I**. It is thought that for C-allylation to occur some mode of phosphine dissociation in species **F** has to take place to allow for the formation of transition state **TS**, in which an intramolecular electrophilic attack at *ortho*-C-H positions of the O-coordinated phenol by the allyl moiety may occur.

As is observed from the experiments, the selectivity for O-allylation (pathway **F** → **G** → **H**) is very high under the optimal reaction conditions. In the previous chapters, it was concluded that restriction of coordination space around the ruthenium(IV) intermediate favors O-allylation and inhibits C-allylation. Complexes with relatively large bite angle diphosphine ligands indeed have restricted coordination space around the Ru(IV) and thus favor the formation of O-allylated product. Although in the present RuCp(PP)-complexes, containing two monodentate phosphine ligands, the P-Ru-P coordination angle can formally not be regarded as a bite angle in the sense of bidentate di-phosphine ligands, it is yet instructive to consider the P-Ru-P coordination angle as such and to compare this angle with the bite angle of bidentate phosphine ligands in corresponding complexes. Indeed, the precursor of the active catalyst, [RuCpCl(PPh$_3$)$_2$], has a P-Ru-P angle of 107° [11], and under the conditions used here it shows high selectivity for O-allylation similar to that of the complexes [RuCp(dppb)](OTs) and [RuCp(dpppe)](OTs) with large bite angle ligands (Table 4.2). Since it is assumed that phosphine dissociation is relatively easy in [RuCp(dppb)](OTs) and especially [RuCp(PPh$_3$)$_2$](OTs) in the Ru(II) oxidation state, it seems counterintuitive that these complexes hardly form C-allylated products and are very selective for O-allylation. However, it must be noted that selectivity in the allylation reaction (i.e. O- vs C-allylation) is determined in the Ru(IV) state; phosphine dissociation is expected to be much less favored here, because of the highly electrophilic character of the Ru(IV) centre. Furthermore, it must be taken into account that these complexes are active at lower reaction temperatures, which also influences the rate of dissociation. It is thus proposed that in species **F** (Scheme 4.3), the phenol molecule will approach the highly electrophilic Ru(IV) centre and enter its coordination sphere to give species **G**, thereby forcing the π-allyl fragment to σ-allyl to maintain an 18 electron species; the proton of the phenol will become extremely acidic in **G** because of the very high Lewis acidity of the Ru(IV) centre. Thus the phenol will be deprotonated, which is followed by a relatively fast reductive elimination induced by the large P-Ru-P angle to give **H**.

It is intriguing to note the striking difference between a Ru(II)- and Ru(IV)-alcoholate species concerning the proposed role and influence of excess of protons (HOTs) on the catalysis and reflecting their vast difference in Lewis acidity. Whereas with Ru(II) species formation of Ru(II)- alcoholate **B** is strongly suppressed by the addition of acid, no negative effect of acid on the formation of Ru(IV)-phenolate species **G** is invoked.

Allyl phosphonium salt formation of an excess of PPh_3 as observed (Scheme 4.2), via the allylation reaction of PPh_3, has mechanistic similarity to the allylation of phenol. However, the fact that coordinated phosphines are not susceptible for allylation to form allyl phosphonium salts, seems to indicate that the free phosphine attacks the Ru(IV)-bound allyl group from outside the coordination sphere. If phenol, similar to PPh_3, also were to attack the Ru(IV) bound π-allyl from outside the coordination sphere one would expect a strong negative order in added acid, as the phenolate concentration outside the coordination sphere will of course be dramatically reduced by protonation. A similar mechanistic detail is proposed for the Tsuji-Trost reaction with palladium, where it is proposed that hard nucleophiles will first coordinate to the metal centre, followed by reductive elimination, while soft nucleophiles such as a phosphine will attack from outside the coordination sphere.[12]

Finally, the observation that a complex containing two monodentate ligands has a much higher activity for the allylation reaction than complexes with bidentate phosphine ligands, seems to indicate that for the rate-determining oxidative addition of allyl alcohol, some mode of dissociation of a phosphine may occur. However, this must be a mode in which the PPh_3 ligand does not fully leave the coordination sphere, since it was shown that free PPh_3 reacts rapidly to form the allyl phosphonium salt, which would lead to rapid deactivation of the catalyst due to PPh_3 consumption. It is thought that the monodentate phosphine ligands with a more flexible coordination configuration probably can easily move aside to accommodate the space needed for approach of the C-O moiety of allyl alcohol and subsequent oxidative addition. A more facile approach of the C-O moiety to the Ru(II) centre with monodentate ligands compared to bidentate ligands is thus believed to be at the basis of the high activity for allylation with the $[Ru(II)Cp(PPh_3)_2]^+$ complex.

4.3 Conclusions

In summary, it has been found that the allyl alcohol isomerization catalyst $[RuCp(PPh_3)_2](OTs)$ can be forced into new reactivity with allyl alcohol. In the presence of acid and at relatively mild temperatures the catalyst is highly active and selective for the O-

allylation of phenols with allyl alcohol, outperforming the catalysts with bidentate phosphine ligands reported in the previous chapters. Very high turnover numbers can be achieved, indicative of a highly stable catalyst.

The observations lead to refinement of some mechanistic details proposed earlier for Ru catalyzed allylation, in particular with respect to catalyst activity and selectivity for O-vs C-allylation of phenols. In the presence of excess of monodentate phosphine ligand and acid rapid allylation of phosphine, yielding allyl phosphonium salts, also takes place. The observations imply similarities, but also distinct differences between the allylation of phenol and that of a phosphine such as PPh_3. The main difference lies in the product forming steps, i.e. the formation of allyl phenyl ether and allyl phosphonium salt, respectively. The formation of allyl phenyl ether requires pre-coordination of phenol at the strongly Lewis acidic Ru(IV)-allyl centre, before reductive elimination of the allyl ether takes place, while the allyl phosphonium salt is formed by attack of the free phosphine from outside the Ru(IV) coordination sphere on the allyl fragment at Ru(IV), followed by protonation.

4.4 Experimental

General remarks. All reactions were performed under an argon atmosphere using standard Schlenk techniques. Solvents were dried and distilled by standard procedures and stored under argon. Triphenylphosphine was commercially available and used as received. $RuCl_3 \cdot 3H_2O$ (Johnson & Matthey) was used as received. [RuCpCl(PPh$_3$)$_2$],[11] [RuCpCl(dppp)][13] (dppp = 1,3-bis[diphenylphosphino]propane) and [RuCpCl(dppb)][14] were prepared according to literature procedures.
^{1}H NMR spectra (300 MHz), and ^{31}P{1H} NMR spectra (121.4 MHz) were measured on a Bruker DPX-300. Chemical shifts are reported in ppm. Proton chemical shifts are relative to TMS, and phosphorus chemical shifts are relative to 85% aqueous H_3PO_4. The spectra were taken at room temperature.

Synthesis of [RuCpCl(dpppe)] (dpppe = bis(diphenylphosphinophenyl) ether). A solution of RuCpCl(PPh$_3$)$_2$ (72 mg, 0.1 mmol) and the bidentate dpppe phosphine ligand (0.1 mmol) in 5 ml toluene was stirred for 16 h at 90 °C. The solution was cooled to room temperature and flushed over a column of silica gel (3 g, d = 1 cm) with 15 ml of toluene to remove the triphenylphosphine. Finally, the orange product was eluted with ethyl acetate until the eluens was colorless. The solution was then concentrated in *vacuo* to approximately 1 ml and the product precipitated with petroleum ether and [RuCpCl(dpppe)] was obtained as a yellow solid in a yield of 69 mg (93%). Anal. Calcd for $C_{41}H_{33}ClOP_2Ru \cdot 0.25$(hexane): C, 67.01; H, 4.83. Found: C, 66.62; H, 4.92. ^{1}H-NMR ($CDCl_3$): δ 7.50 (m, 2H, ArH), 7.36 (m, 8H, ArH), 7.26-7.13 (m, 8H, ArH), 7.01 (m, 4H, ArH), 6.92-6.90 (m, 2H, ArH), 6.84-6.71 (m, 4H, ArH), 4.10 (s, 5H, Cp). ^{31}P-NMR ($CDCl_3$): δ 44.6 (s).

General procedure for catalytic reactions. 2.5 mmol of 4-*tert*-butylphenol (or another nucleophilic substrate if indicated), 2.5 μmol of the ruthenium-chloride catalyst precursor complex, 5.0 μmol of AgOTs (to displace chloride anions with tosyl through formation of

AgCl) and 0.05 mmol of HOTs were charged into the reaction vessel and flushed with argon. Degassed and dried toluene was added (2.5 ml) and the mixture was stirred for five minutes. Allyl alcohol was added (5 mmol) and the reaction was stirred at 60 °C. Samples were taken at certain time intervals with an airtight syringe and analyzed by gas chromatography.
The spectroscopic data of allyl phenyl ether,[15] allyl 2,4,6-trimethylphenyl ether[16] and allyl phenyl sulfide[17] corresponded with the data reported in literature.

High turnover number experiments. The catalyst amount ([RuCpCl(PPh_3)$_2$] and AgOTs) were kept constant, while increasing the amounts of the reactants (4-*tert*-butylphenol and allyl alcohol), acid (HOTs) and solvent (toluene) by a factor 20. A similar reaction was conducted, but the amount of ruthenium complex was reduced to 0.25 μmol. After 72 hours, a turnover number of 75,000 was reached.

GLC Method. Quantitative gas liquid chromatography analyses were carried out on a Varian CP-3800 apparatus equipped with a VF-1 ms (25 m × 0.25 mm) column with decane as internal standard. The temperature gradient used was: isothermal for 5 min at 40 °C, heating 10 °C/minute to 250 °C and finally isothermal for 5 min at 250 °C.

Phosphonium salt formation. 2.5 μmol of [RuCpCl(PPh_3)$_2$], 5 μmol of AgOTs, 0.05 mmol of triphenylphosphine and 0.05 mmol of HOTs were charged into the reaction vessel and flushed with argon. Degassed and dried toluene was added (2.5 ml) and the mixture was stirred for five minutes. Allyl alcohol was added (5 mmol) and the reaction was stirred at 60 °C for five minutes. Reaction was cooled to room temperature and the mixture was concentrated *in vacuo* to yield a colorless oil in 24 mg (100%). ^{1}H-NMR ($CDCl_3$): δ 7.76-7.62 (m, 17H, ArH), 7.06 (d, 2H, *J* = 7 Hz, ArH), 5.73-5.59 (m, 1H, H-allyl), 5.40 (dd, 1H, *J* = 6 Hz, 30 Hz, =C<u>H</u>H), 5.35 (dd, 1H, *J* = 6 Hz, 24 Hz, =CH<u>H</u>), 4.38 (dd, 2H, *J* = 9 Hz, 12 Hz, CH_2), 2.30 (s, 3H, Me). ^{31}P{^{1}H}-NMR ($CDCl_3$): δ 21.6 (s).

Kinetic data on experiments with extra triphenylphosphine addition. The general procedure for catalytic reactions was followed, but with addition of the indicated amount of triphenylphosphine to the mixture prior to flushing with argon.

Procedure for "second batch" experiments. The general procedure for catalytic reactions was followed, but after three hours, a second batch of substrates was added (2.5 mmol of 4-*tert*-butylphenol and 5.0 mmol of allyl alcohol). Samples were taken at one and three hours after addition of the first batch and at one and three hours after addition of the second batch (four hours total reaction time).

4.5 References

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5

Scope of the allylation reaction with $[RuCp(PP)]^+$ catalysts: changing the nucleophile or allylic alcohol

Abstract
The scope of the allylation reaction for other substrates is explored. Aliphatic alcohols are successfully allylated with allyl alcohol or diallyl ether using $[RuCp(PP)]^+$ catalysts, obtaining high selectivity for the alkyl allyl ether. The reactivity of aliphatic alcohols is in the order of primary > secondary >> tertiary. The tertiary alcohol 1-adamantanol reacts extremely slow in the absence of strong acid, but when HOTs is added, reasonable yields of 1-adamantyl allyl ether are obtained. The alkyl allyl ether is found to be the thermodynamically favored product over diallyl ether. Apart from alcohols, also thiols and indole are efficiently allylated, while aniline acts as a catalyst inhibitor. Allylation reactions with alkyl substituted allylic alcohols give products with retention of the substitution pattern. It is proposed that a Ru(IV) σ-allyl species plays a key role in the mechanism of such allylations.

5.1 Introduction

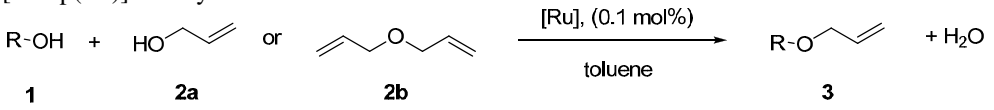
The use of $[RuCp(PP)]^+$ complexes in the catalytic allylation of phenols with allyl alcohol has been demonstrated (Chapter 2-4). It was observed that during this process, allyl alcohol also reacts with itself as the nucleophilic alcohol to form diallyl ether. It is therefore interesting to broaden the range of substrates, using both alcoholic as well as non-alcoholic nucleophiles, in a catalytic reaction with allyl alcohol as the allylating agent, in the presence of the catalysts presented in the previous chapters.

Allylation of aliphatic alcohols to form alkyl allyl ethers is commonly carried out with allyl halides or acetates,[1-3] but also allyl alcohol can be used as the allylating agent and a few examples have been reported.[4-6] Unlike the allylation of phenols, where O- and C-allylation can occur, the allylation of aliphatic alcohols is always selective for allyl ether formation. For the cross-allylation of alcohols with allyl alcohol, the presence of diallyl ether is generally not reported, although it is most likely formed somewhere during the reaction, as has been demonstrated[6,7] in literature and in previous chapters.

In Chapters 2 and 3, the allylation of phenols with allyl alcohol in the absence of strong acid is described. This system is unique, because in all of the reported allylation reactions with Ru-complexes as catalyst and allyl alcohol as allylating agent, strong acids are present to promote the reactivity of allyl alcohol.[4,8,9] One could imagine the phenol to act as an acid (pKa =10) to activate allyl alcohol for allylation. Given the low acidity of aliphatic alcohols, it would be interesting to see how the allylation of aliphatic alcohols proceeds with a similar catalytic system in the absence of acid. Apart from alcohols, the scope of the $[RuCp(PP)]^+$-catalyzed reactions is expanded by testing other substrates often used in allylation reactions, like amines,[10,11] indole,[9] thiols[12] and activated diketones.[13]

Apart from allyl alcohol as allylating agent, substituted allylic alcohols have also been used in allylation reactions.[12,14] Unlike reactions with allyl alcohol, substituted allyl alcohols always react with a certain regioselectivity, which depends on the catalyst and structure of the substrate and such reactions often lead to interesting clues for the mechanism. For ruthenium catalysts active in the allylation reaction, often the branched product is favored over the linear product.[12,14-16] The reactivity of several substituted allylic alcohols in Ru-catalyzed allylations is reported in this chapter.

Table 5.1. Allylation of aliphatic alcohols with either allyl alcohol or diallyl ether in the presence of $[RuCp(PP)]^+$ catalysts. [a]



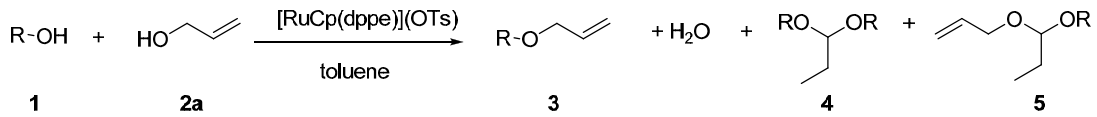
entry	R =	allyl donor	yield of **3** (%)
1[b]	1-octyl	2a	52
2	1-octyl	2a	100
3	1-butyl	2a	100
4	Ethyl	2a	86
5[c]	1-octyl	2b	84
6[c]	1-butyl	2b	88
7[c]	Ethyl	2b	97
8[c]	1-octyl	allyl butyl ether	42

[a] Reaction conditions: ratio aliphatic alcohol/allyl alcohol/[RuCpCl(*o*-EtOdppe)]/AgOTs = 1000/1000/1/2, 100 °C, 2 h, toluene.
[b] [RuCpCl(dppe)] was used as catalyst precursor
[c] Reaction conditions: ratio aliphatic alcohol/**2b** (or **3b**)/[RuCpCl(*o*-EtOdppe)]/AgOTs = 1000/1000/1/2, 100 °C, 2 h.

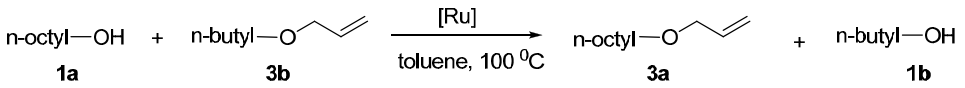
5.2 Results and discussion

5.2.1 Allylation reactions of alcohols with allyl alcohol as the allyl donor

[RuCp(dppe)](OTs) and [RuCp(*o*-EtOdppe)](OTs), the most active catalysts in the absence of strong acid reported in Chapter 2, were explored as catalysts in the allylation of aliphatic alcohols. The aliphatic primary alcohol 1-octanol was used as a substrate and it was observed that both the catalysts [RuCp(dppe)](OTs) and [RuCp(*o*-EtOdppe)](OTs) convert 1-octanol into the allyl octyl ether. (Table 5.1; entry 1 and 2). During the reaction, diallyl ether is formed, as described in Chapter 2, but in much smaller amounts (< 10%) compared to the reaction with phenols and it is reacted away after approximately one hour. Striking is that the reaction with $[RuCp(o\text{-EtOdppe})]^+$ as the catalyst shows a much higher conversion after 2 hours than when $[RuCp(dppe)]^+$ is used. After longer reaction times (> 2 h), using the catalyst [RuCp(dppe)](OTs) (entry 1) propionaldehyde dioctyl acetal **4** and propionaldehyde octyl allyl acetal **5** were formed, most likely due to the slow, but irreversible isomerization of allyl alcohol into propionaldehyde (propanal) and the fast subsequent acetalisation reaction with an alcohol (Scheme 5.1). In the reactions using [RuCp(*o*-EtOdppe)](OTs) as the catalyst these



Scheme 5.1. Formation of allyl ether and acetals from aliphatic alcohols **1** and allyl alcohol **2a**.

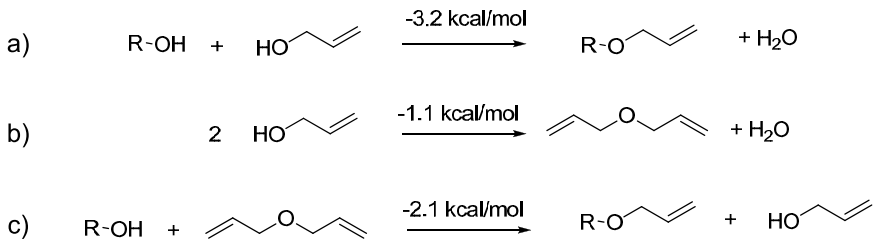


Scheme 5.2. Transallylation between 1-octanol and allyl butyl ether.

side products are not observed, indicating that isomerization to propanal does not occur. The observation that introduction of *ortho*-substituted phenyl rings on phosphorous blocks the isomerization reaction was also observed by van der Drift *et al*.,[5] for isomerization of 3-buten-2-ol into the corresponding carbonyl compound. Therefore, of these two catalysts, [RuCp(*o*-EtOdppe)](OTs) was further explored.

The observation that a high yield of allyl octyl ether is obtained after longer reaction times and no diallyl ether remains is remarkable. Reactions with other primary alcohols like 1-butanol (entry 3) and ethanol (entry 4) also results in a high yield for the alkyl allyl ether. Diallyl ether can even be used as the allyl donor, forming the allyl octyl ether in high yield (Table 5.1; entries 5-7). A thermodynamical preference for the alkyl allyl ether seems to be present and when the energy difference between substrates and products is calculated using Hartree-Fock methods for the three reactions (Scheme 5.3), indeed a slightly larger energy gain is found for alkyl allyl ether formation with allyl alcohol as allylating agent (-3.2 vs. -1.1 kcal/mol). The allylation reaction with diallyl ether as allylating agent thus also has a negative ΔE. Although the energy differences are small and activation barrieres were not calculated, a thermodynamic preference for alkyl allyl ether formation is held reponsible. The low polarity of the reaction mixture and resulting efficient separation of water from the reaction mixture as a separate phase when aliphatic alcohols are used, promote the formation of alkyl allyl ethers in high yields.

When allyl butyl ether is reacted with 1-octanol (Table 5.1; entry 8; Scheme 5.2), indeed transallylation occurs until an equilibrium is reached, indicating that the formation of allyl alkyl ethers is reversible, but the reaction does not go to completion towards allyl octyl ether



Scheme 5.3. Energy differences for diallyl ether, alkyl allyl ether formation with allyl alcohol and alkyl allyl ether formation with diallyl ether.

Table 5.2. Allylation of secondary and tertiary alcohols with allyl alcohol (**2a**) as allylating agent in the presence of [RuCp(*o*-EtOdppe)](OTs). [a]

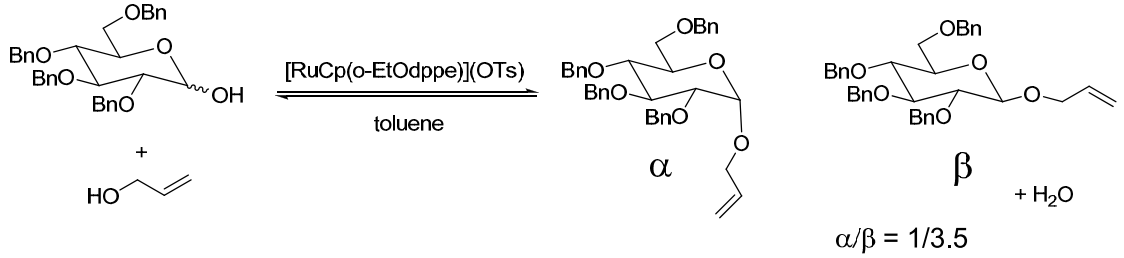
entry	alcohol	rate constant k (h^{-1})[b]	yield of **3** (%)
1	1-octanol	4.61	100
2	cyclohexanol	1.43	75
3	2-adamantanol	1.12	82
4	1-adamantanol	0.02	10
5[c]	1-adamantanol	0.78	52
6	2,3,4,6-tetra-O-benzyl-D-glucose	-	80[d]
7[e]	4-*tert*-butylphenol	1.02	68

[a] Reaction conditions: ratio aliphatic alcohol/allyl alcohol/[RuCpCl(*o*-EtOdppe)]/AgOTs = 1000/1000/1/2, 100 °C, toluene, 2 h.
[b] k = - ln{1 -conversion(%)/100]/t} for t = 0.5 h
[c] Reaction conditions: Ratio aliphatic alcohol/allyl alcohol/[RuCpCl(PPh_3)$_2$]/AgOTs/HOTs = 1000/2000/1/2/20, 60 °C, toluene , 2 h
[d] isolated yield
[e] results taken from Chapter 2

due to the absence of a thermodynamical energy preference.

Apart from these primary alcohols, also secondary and tertiary alcohols were reacted with allyl alcohol in the presence of [RuCp(*o*-EtOdppe)](OTs). The results are shown in Table 5.2. Comparing the allylation of an aliphatic secondary alcohol with a primary alcohol (entry 1), it is clearly shown by looking at the calculated (first order) rate constants, determined from the conversion after 30 minutes reaction time, that the reactivity of secondary alcohols is considerably lower. (cf entry 1 with (entries 2 and 3). The rate constants for secondary alcohols are comparable to that of 4-*tert*-butylphenol (entry 7). Tertiary alcohol 1-adamantanol reacts very slowly (entry 4) and the rate constant for allylation is almost 2 orders of magnitude lower than that of reactions with the secondary alcohols. To obtain a higher conversion of 1-adamantanol, the highly reactive catalyst [RuCp(PPh_3)$_2$](OTs) in the presence of strong acid was employed (entry 5) and a good yield of 1-adamantyl allyl ether was obtained.

A carbohydrate was tested for its reactivity in allylation with allyl alcohol, since the allyl group is an often used protecting group in carbohydrate chemistry.[17] The sugar 2,3,4,6-tetra-O-benzyl-D-glucose was used (entry 6), which has benzyl protection groups at all the



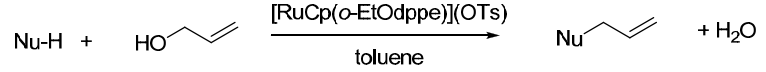
Scheme 5.4 Ru-catalyzed allylation of 2,3,4,6-tetra-O-benzyl-D-glucose with alcohol and it selectivity.

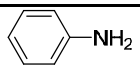
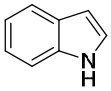
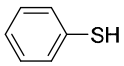
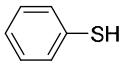
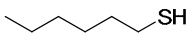
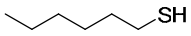
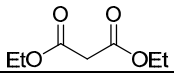
hydroxyl groups except for the anomeric position. The reaction shows a high conversion towards the allyl ether. An α to β ratio of 1/ 3.5 (Scheme 5.4) was found as was deduced from the ^{1}H-NMR spectra.[18,19] The preference for the sterically less hindered β-product is most likely induced by the relative sterically crowded catalyst.

5.2.2 Other nucleophilic substrates in allylation reactions

Apart from aliphatic alcohols as the nucleophilic substrate, also non-alcoholic nucleophiles were explored for their reactivity in the allylation reaction (Table 5.3). Aniline (entry 1) proved to be unreactive under these reaction conditions. Diallyl ether formation is also not observed, indicating inhibition of the catalyst. The non-nucleophilic N-containing substrate indole is efficiently allylated, resulting in the C-allylated product with the allyl group on the C_3-position (entry 2). Interestingly, as was described in Chapter 4, indole could not be allylated with the catalyst [RuCp(PPh_3)$_2$](OTs), which needs the presence of *p*-toluenesulfonic acid for activity on allylation reactions. This strong acid reacts with indole, decreasing the acidity of the reaction mixture and thus deactivating the catalyst for allylation reactions. Isomerization of allyl alcohol into propanal is observed in this case. The catalysts [RuCp(*o*-EtOdppe)](OTs) does not require the presence of such an acid and therefore efficiently catalyzes the allylation of indole. Thiols were investigated for their reactivity with

Table 5.3. Allylation of nucleophilic substrates with allyl alcohol (**2a**) as allylating agent in the presence of [RuCp(*o*-EtOdppe)](OTs).[a]



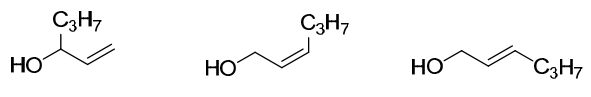
entry	Nu-H	reaction time (h)	conversion of NuH (%)
1		2	0
2		2	85
3		2	38
4		20	48
5		2	12
6		20	78
7		2	0

[a] Reaction conditions: Ratio aliphatic alcohol/allyl alcohol/[RuCpCl(*o*-EtOdppe)]/AgOTs = 1000/1000/1/2, 100 °C, toluene.

allyl alcohol in the presence of [RuCp(*o*-EtOdppe)]$^+$ and proved to be suitable substrates for these type of reactions. The reaction of thiophenol with allyl alcohol (entry 3) is completely selective for allyl phenyl sulfide formation and C-allylated products are not observed. The conversion after 2 hours is only 38% and after 20 hours (entry 4) has not increased much. An equilibrium seems to be reached, like in the allylation of phenols. The conversion of *n*-hexanethiol after 2 hours (entry 5) is even lower than that of thiophenol, but after 20 hours has increased significantly (entry 6). Finally, diethylmalonate is found not to be reactive, most likely due to the very low nucleophilicity of the backbone CH_2-moiety, preventing its activation towards attack of the electrophilic Ru centre. Only diallyl ether is formed.

5.2.3 Allylation reaction with substituted allylic alcohols as allyl donors

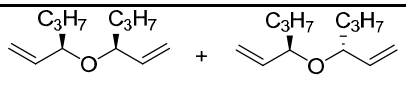
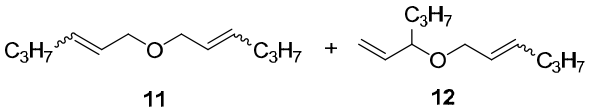
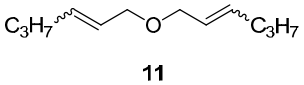
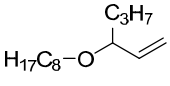
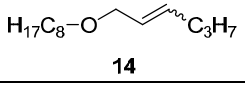
Apart from broadening the scope on the nucleophilic substrates, also substituted allylic alcohols were investigated on their reactivity in the ruthenium-catalyzed system. Different substitution patterns were explored and both branched as well as linear, cis and trans allylic alcohols were used (Figure 5.1; compounds **6**-**8**). The reactions with [RuCp(*o*-EtOdppe)](OTs) as catalyst and **6**-**8** as substrates showed no conversion of the allylic alcohols. By adding strong acid, some conversion of **6**-**8** is observed, but the *ortho*-substituted catalysts are relatively unstable over longer periods of time (after 3 hours) in the presence of acid, as was already reported in Chapter 3. In Chapter 4, a catalyst system based on [RuCp(PPh_3)$_2$]$^+$ and HOTs proved highly active and stable as allylation catalysts with allyl alcohol at 60 °C. Therefore the complex [RuCp(PPh_3)$_2$]$^+$ in the presence of HOTs was also used as the catalyst system for allylation of alcohols with substituted allylic alcohols. First, homo-coupling of substituted allylic alcohols is discussed while subsequently, allylation of 1-octanol with these allylic alcohol substrates is addressed. The results are shown in Table 5.4.
For the reaction with **6** as the substrate, only branched diasteromeric diallyl ethers **9** and **10** are formed. Both diastereoisomers are detected by GC in a ratio of 1/1. The terminal olefin moiety is identified by ^{1}H-NMR spectroscopy. Reactivity of **6** is lower than that of the non-substituted allyl alcohol **2a**, probably for steric reasons. A conversion of only 51% is obtained after 6 hours (Table 5.4; entry 1). The reactivity of the allylic alcohol **7** carrying an internal



6 **7** **8**

Figure 5.1. Substituted allylic alcohols employed in allylation reaction the presence of Ru-catalysts.

Table 5.4. Allylation reactions with substituted allylic alcohols as allylating agent in the presence of $[RuCp(PPh_3)_2](OTs)$ and HOTs [a]

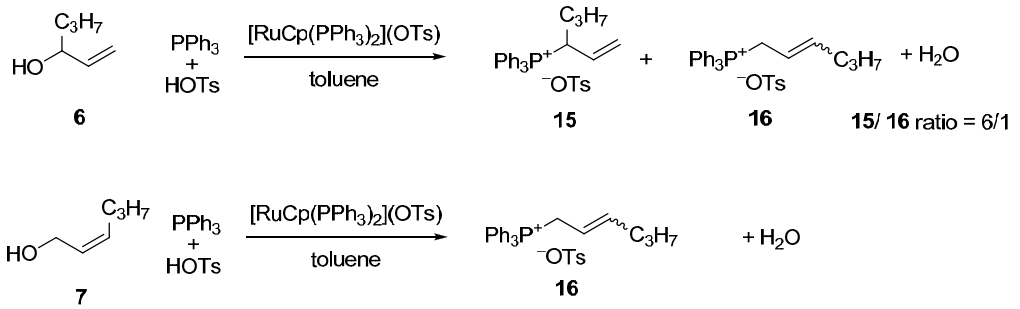
entry	substrate	conversion of **6**-**8** (%)	products formed	selectivity to products (%)
1	**6**	51	 **9** + **10**	50 (**9**) 50 (**10**)
2	**7**	29	 **11** + **12**	75 (**11**) 25 (**12**)
3	**8**	3	 **11**	100 (**11**)
4	**6** + 1-octanol	81	 **13**	100 (**13**)
5	**7** + 1-octanol	31	 **14**	100 (**14**)

[a] Reaction conditions: ratio aliphatic alcohol/allyl alcohol/$[RuCpCl(PPh_3)_2]$/AgOTs/HOTs = 1000/2000/1/2/20, 60 °C, toluene, 6 h.

cis-olefin moiety is again lower, resulting in only 29% conversion after 6 hours (entry 2). The major product is the linear product **11** (75%) with product **12** (25%) as the minor component. Cis and trans-isomers could not be properly separated and indentified. Compound **8**, with an internal *trans*-olefin moiety is the least reactive and only 3% conversion is observed after 6 hours (entry 6). The only product formed in measurable quantity, is compound **11**.

Allylic alcohols **6** and **7** have also been applied as the allylation source for the allylation of 1-octanol. Compounds **8** was not further investigated, due to its very low reactivity. When **6** was reacted with 1-octanol, the alkyl allyl ether **13** was formed (entry 4), with a branched allyl moiety as observed by ^{1}H-NMR spectroscopy. The reaction between **7** and 1-octanol only yields linear product **14** (entry 5). Conversion of **6** after 6 hours, is 81% which is significantly higher than that in the diallyl ether formation. The reaction of **7** with 1-octanol is also highly selective, but in this case for the linear product **14**. Branched components are not observed, unlike the self-condensation reaction described in entry 2.

Apart from an allylation of alcohols as substrates, also the allylation of triphenylphosphine with **6** and **7** was investigated, similar to that described in Chapter 4. After a reaction time of 1 hour, the triphenylphosphine was fully converted and phosphonium salts were formed. The formed products were isolated with preparative HPLC and analyzed with NMR (^{1}H and ^{31}P) and mass spectrometry. For the reaction with **6**, mainly the branched phosphonium salt **15** is formed (Scheme 5.5), while in the reaction with **7**, the linear product **16** is formed with high 100% selectivity.



Scheme 5.5. Allylation of triphenylphosphine with **6** and **7** as allylating agent in the presence of $[RuCp(PPh_3)_2](OTs)$.

5.2.4 Mechanistic considerations

The difference in the reactivity of $[RuCp(o\text{-EtOdppe})]^+$ and $[RuCp(dppe)]^+$ for allylation (Table 5.1) and the formation of acetals in the reaction with $[RuCp(dppe)]^+$ is striking. The acetals are formed via the reaction of propanal with the aliphatic alcohol and allyl alcohol itself. Apparently, under the reaction conditions used, $[RuCp(dppe)]^+$ catalyzes the isomerization of allyl alcohol with formation of propanal, besides the allylation reaction. However, in Chapter 2 $[RuCp(dppe)]^+$ has also been reported as active catalyst in the allylation of phenol, but aldehyde or acetal formation was not observed. Lack of aldehyde formation in this case can probably be attributed to the acidity of phenol, preventing allylic alcoholate formation and subsequent propanal formation, as was discussed in Chapter 4. However, $[RuCp(o\text{-EtOdppe})]^+$ is expected also to form a Ru-alcoholate species under neutral conditions, but here the increased steric hindrance of the *o*-EtO-aryl groups at P around the Ru(II) centre probably prevents β-H elimination as an essential intermediate step[5] in propanal formation. Acidic protons are apparently not stricktly needed for the activation of allyl alcohol as allylating agent with a $[RuCp(o\text{-EtOdppe})]^+$ catalyst, since aliphatic alcohols are not acidic enough (pKa ~ 16) to protonate coordinated allyl alcohol.

Apart from the aliphatic alcohols, other nucleophilic substrates are efficiently allylated. The difference in reactivity between aniline and indole is striking. Aniline acts as a catalyst inhibitor, since diallyl ether formation is also not observed. It is thought that a strong coordination of aniline to the Ru(II) species hinders coordination of allyl alcohol via its olefin moiety and thus prevents subsequent oxidative addition and allylation reactions. Indole's NH moiety is much less nucleophilic than aniline and thus is not expected to coordinate to the Ru(II) species. Only after formation of a highly reactive Ru(IV) allyl species is indole activated to form 3-allylindole. The C_3-position apparently is more nucleophilic than the

nitrogen atom as has been observed previously.[14] In Chapter 4 it was shown that indole could not be allylated with an acidic $[CpRu(PPh_3)_2]^+$ catalyst system, since the acid, necessary for activity in allylation, is neutralized by indole's NH moiety. So although indole's NH moiety does not seem to coordinate to a Ru(II) species, it is basic enough to deprotonated the strong acid HOTs.

Catalytic activity is nonetheless observed, albeit for allyl alcohol isomerization, indicating that indole does not act as an inhibitor.

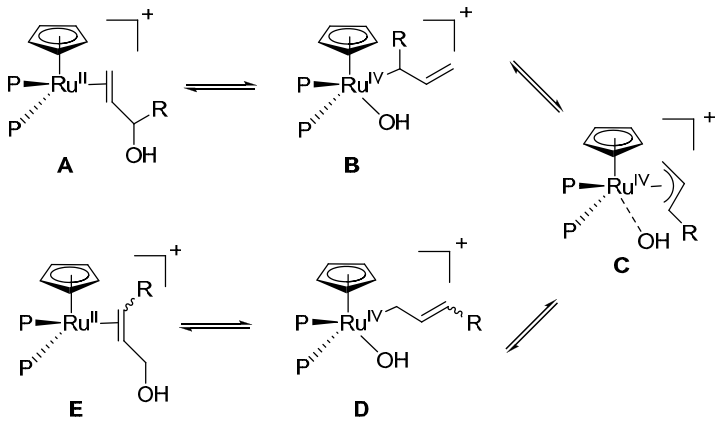
Thiols are demonstrated to react with complete selectivity for the S-allylated product. The higher nucleophilicity of thiophenolate as compared to phenolate most likely promotes formation of allyl sulfides, but also the increase in size of the nucleophilic donor atom may cause the high selectivity, as it was observed in the previous chapters that restricted space around the Ru-center favors formation of allyl ethers.

Alkyl substitution at the allylic alcohol moiety influences their performance in the allylation reaction of alcohols very significantly, both with respect to their reactivity as well as to the possibility of achieving a certain regio-selectivity with which the allylation products are produced.

As can be seen from Table 5.4, for allyl alcohols with an alkyl substituent, the reactivity appears highly dependent on the position of the olefin moiety. Allylic alcohol **6**, with a terminal olefin shows the highest reactivity, followed by that with an internal cis-olefin **7**, while the allylic alcohol with an internal trans-olefin moiety **8** is hardly reactive. The coordination of a terminal olefin moiety to a Ru(II) complex has been shown to be strongly favored over that of an internal olefin.[5] Compound **6** has the least steric hindrance around its olefin moiety, while for internal olefinic moieties, a cis-configuration is sterically less demanding than a trans-configuration, since its substituents point in the same direction, leaving the olefin relatively free on one side for coordination.

The relative order of reactivity suggests that pre-coordination of the olefinic moiety in the allylic alcohol plays an important role in the rate-determining oxidative addition pathway of the allylic alcohol (or ether) at the Ru(II) centre. It is thought that pre-coordination brings about close proximity of the C-O bond to Ru(II), required for the two-electron transfer from Ru(II) to the allyl- and OH (OR) fragments at Ru.

As discussed before (Chapter 2 and reference 20), it is thought that the *initial* oxidative addition product constitutes a Ru(IV)-σ- allyl species in which the OH^- (or OR^-) moiety is still coordinated to the Ru(IV). We have earlier proposed in Chapter 2 and 3 that depending on the coordination strength of the phosphine ligand and the hydroxide anion, or alcoholate anionic



Scheme 5.6. Possible intermediates for reactions of alkyl substituted allyl alcohols (R = alkyl chain).

moiety to the Ru(IV) centre, Ru(IV)(σ-allyl) species may rearrange to a Ru(IV)(π-allyl) species. With substituted allylic alcohols, un-symmetric Ru-π-allyl species can be generated that will affect both the kinetics of σ-allyl→ π-allyl re-arrangement as well as the relative stability of Ru-σ-allyl vs Ru-π-allyl species.

The reactions of substituted allylic alcohols **6**-**8** generally show preference for retention of the original substitution pattern of the corresponding allylic alcohol. This phenomenon has been described as the "memory effect" and multiple explanations have been reported for Tsuji-Trost-type reactions.[21-24] For Ru-based catalysts, this effect, however, has not been reported thus far and mostly a preference for the branched isomer is reported, starting from either a branched or a linear allylic substrate.[14,15] The "memory effect" observed in this chapter, indicates that the isomerization of an initially formed branched σ-allyl to ultimately a linear σ-allyl species, –such as may occur with substrate **6**, (Scheme 5.6 from **B** to **D**) or vice versa, most likely via a π-allyl species (**C**)–, is a relatively slow process relative to reductive elimination (from **B** to **A** or **D** to **E**). However, in the homoallylic coupling reaction with substrate **7** (Table 5.4; entry 2) also a minor quantity of branched isomer is formed, which must mean that a Ru(IV)(π-allyl) species is formed during the catalytic cycle. Intriguingly, when compound **7** is reacted with 1-octanol, only the linear product **14** is formed, indicative of a faster reductive elimination with 1-octanol as nucleophilic substrate as compared to reductive elimination when **7** is the nucleophile. *cis* and *trans* isomers could not be efficiently separated by GLC and therefore exact data on their relative formation rates cannot be presented. A *cis-trans* isomerization must occur via a π-allyl species **C** and since their formation from the initially formed σ-allyl species **D** seems to be relatively slow, retention of either the *cis*- or *trans* isomer is highly likely.

Triphenylphosphine is a soft nucleophile and in analogy with the Tsuji-Trost mechanism[25], an attack from outside the coordination sphere of triphenylphosphine is proposed for the Ru-based catalyst described in this chapter. Again, a preference for retention of the original substitution pattern is observed. The reaction of triphenylphosphine with **6** mainly forms the branched phosphonium salt, but linear product **16** is also observed as the minor component. This could indicate that nucleophilic attack of PPh_3 on the Ru(IV)(π-allyl) species can compete with attack on the Ru(IV)(σ-allyl) species. Possibly, σ- to π-allyl isomerization occurs at a comparable rate as nucleophilic attack of PPh_3. Such a competition is not observed for the reaction of PPh_3 with with the linear allylic alcohol **7**, indicative of a slower linear-σ-allyl → π-allyl vs branched-σ-allyl → π-allyl isomerization at the Ru(IV) intermediate.

5.3 Conclusions

It is shown that apart from phenols, primary, secondary and even tertiary aliphatic alcohols can be successfully allylated with allyl alcohol or diallyl ether as the allylating agent using $[RuCp(o\text{-EtOdppe})]^+$. This makes it the first catalytic system, which efficiently performs allylation of primary, secondary and tertiary alcohols with allyl alcohol as the allylating agent. A thermodynamical preference for an alkyl allyl ether over a diallyl ether is found, explaining the high selectivity towards alkyl allyl ethers over diallyl ether. Apart from alcohols as nucleophilic substrates, also thiols, both aromatic and aliphatic, and indole are efficiently allylated. Substituted allylic alcohols with a terminal olefin moiety have a higher reactivity than allylic alcohols with an internal olefin moiety. Of the latter, (*Z*)-allylic alcohols are more reactive than (*E*)-allylic alcohols. The substitution pattern (branched or linear) of substituted allyl alcohols remains mostly unchanged after reaction, indicating a relatively slow σ-π allyl-rearrangement relative to reductive elimination at the Ru(IV) intermediate.

5.4 Experimental

General remarks. All reactions were performed under an argon atmosphere using standard Schlenk techniques. Solvents were dried and distilled by standard procedures and stored under argon. The alcohols 1-octanol, 1-butanol and ethanol were commercially available and distilled prior to use. The alcohols cyclohexanol, 1-adamantanol, 2-adamantanol and 2,3,4,6-tetra-O-benzyl-D-glucose were commercially available and used as received. $[RuCpCl(PPh_3)_2]$,[26] [RuCpCl(dppe)][27] and [RuCpCl(*o*-EtOdppe)] (Chapter 2) were synthesized as reported. Mass spectrometry was performed on a Finnigan MAT 900 equipped with an electrospray interface. ^1H NMR spectra (300 MHz), ^{13}C-NMR (75.5 MHz) and $^{31}P\{^1H\}$NMR spectra (121.4MHz) were measured on a Bruker DPX-300. Chemical shifts are reported in ppm. The spectra were taken at room temperature.

General procedure for catalytic reactions. 2.5 mmol of alcohol, 0.0025 mmol of the ruthenium complex and 0.005 mmol of AgOTs were charged into the reaction vessel and flushed with argon. Degassed and dried toluene was added (2.5 mL) and the mixture was stirred for five minutes. Allyl alcohol or diallyl ether was added (2.5-5 mmol) and the reaction mixture was stirred at the indicated temperature. Samples were taken at certain time intervals with an airtight syringe and analyzed by gas chromatography. The products were isolated by means of fractional distillation and characterized by ^{1}H-NMR, ^{13}C-NMR and mass spectrometry. The spectroscopic data of the products allyl octyl ether,[28] allyl butyl ether,[29] allyl ethyl ether,[30] allyl cyclohexyl ether,[28] 3-allylindole,[31] allyl phenyl sulfide,[32] and allyl *n*-hexyl sulfide[33] were in agreement with the data found in literature.

GLC method. Quantitative gas liquid chromatography analyses were carried out on a Varian CP-3800 apparatus equipped with a VF-1ms (25 m × 0.25 mm) column with decane or tetradecane as internal standard. The temperature gradient used was: isothermal for 5 minutes at 40 °C, heating 10 °C/ minute to 250 °C and finally isothermal for 5 minutes at 250 °C.

Formation of acetals 4 and 5 (mixture of products). 2.5 mmol of 1-octanol, 2.5 mmol of allyl alcohol, 2.5 μmol of RuCp(dppe)Cl and 5 μmol of AgOTs were charged into a reaction vessel and flushed with argon. 2.5 mL of degassed toluene was added and the mixture was stirred at 100 °C. ^{1}H-NMR ($CDCl_3$): δ 5.94-5.86 (m, H-allyl), 5.21 (dd, *J* = 4 and 9 Hz, H-allyl), 4.15-3.97 (m, CH_2 allyl), 3.54 (m, CH_2), 3.38 (m, CH_2), 1.63-1.26 (m, CH_2), 0.93-0.88 (m, CH_3). ^{13}C-NMR ($CDCl_3$): δ 134.8 (CH-allyl), 116.4 (=CH_2), 104.2 (OCHO), 66.0 (CH_2), 65.1 (CH_2), 31.9 (CH_2), 30.5 (CH_2), 29.6 (CH_2), 27.5 (CH_2), 26.4 (CH_2), 19.3 (CH_2), 13.8 (CH_3), 8.9 (CH_3). MS (ESI) *m/z* (compound **4**) = 301.4 $[M+H]^+$, 271.5 $[M-C_2H_5]^+$. MS (ESI) *m/z* (compound **5**) = 229.3 $[M+H]^+$, 199.8 $[M-C_2H_5]^+$.

1-allyl-2,3,4,6-tetra-O-benzyl-α-D-glucopyranoside and 1-allyl-2,3,4,6-tetra-O-benzyl-β-D-glucopyranoside (mixture of products). The general procedure for catalytic reaction was followed, with the difference that purification of the product was not performed by means of distillation, but the after evaporation of the reaction mixture to dryness, *n*-hexane was added to the mixture. This caused precipitation of the starting material, which was removed by filtration and the resulting filtrate was concentrated to yield a mixture of the products. The ^{1}H-NMR spectroscopic data of 1-allyl-2,3,4,6-tetra-O-benzyl-α-D-glucopyranoside[18] and 1-allyl-2,3,4,6-tetra-O-benzyl-β-D-glucopyranoside[19] were in agreement with the data found in literature.

Allyl 1-adamantyl ether. ^{1}H-NMR ($CDCl_3$): δ 5.97-5.86 (m, 1H, H-allyl), 5.26 (dd, 1H, *J* = 3 and 17 Hz, H-allyl), 5.11 (dd, 1H, *J* = 3 and 9 Hz, H-allyl), 3.97 (d, 2H, *J* = 5 Hz, OCH_2), 2.15-2.13 (m, 3H, CH), 1.78-1.76 (m, 6H, CH_2), 1.61-1.56 (m, 6H, $C\underline{H_2}CO$). ^{13}C-NMR ($CDCl_3$): δ 136.4 (=CH), 115.2 (=CH_2), 68.2 ($O\underline{C}CH_2$), 41.4 (CH_2), 36.3 (CH_2), 30.4 (CH). MS (ESI) *m/z* = 193.37 $[M+H]^+$.

Allyl 2-Adamantanyl ether. ^{1}H-NMR ($CDCl_3$): δ 6.02-5.91 (m, 1H, H-allyl), 5.29 (dd, 1H, *J* = 3 and 18 Hz, H-allyl), 5.13 (dd, 1H, *J* = 3 and 9 Hz, H-allyl), 4.00 (d, 2H, *J* = 3 Hz, OCH_2-allyl), 3.49-3.46 (m, 2H, OCH_2), 2.17-2.08 (m, 3H, H-Ada), 1.86-1.78 (m, 6H, H-Ada), 1.76-1.63 (m, 6H, H-Ada). ^{13}C-NMR ($CDCl_3$): δ 136.6 (CH=), 116.6 (=CH_2), 81.8 (CHO), 69.1 (CH_2O), 38.4 (CH_2), 32.7 (CH), 28.3 (CH_2). MS (ESI) *m/z* = 193.10 $[M+H]^+$.

General procedure for reactions with alkyl substituted allyl alcohols. 0.0025 mmol of the ruthenium complex $[RuCpCl(PPh_3)_2]$, 0.005 mmol of AgOTs and 0.05 mmol of HOTs were

charged into the reaction vessel and flushed with argon. Degassed and dried toluene was added (2.5 ml) and the mixture was stirred for five minutes. Allylic alcohols **6**-**8** were added (2.5 mmol) and the reaction mixture was stirred at 60 °C. Samples were taken at certain time intervals with an airtight syringe and analyzed by gas chromatography. The products (product mixtures) were isolated by means of extraction with *n*-hexane from 10% aqueous NaOH and subsequent distillation and characterized by ^{1}H-NMR spectroscopy and mass spectrometry.

Dihex-1-en-3-yl ether (mixture of diastereoisomers 9 and 10). ^{1}H-NMR ($CDCl_3$): δ 5.87-5.81 (m, 2H, CHC<u>H</u>=), 5.19 (dd, 2H, *J* = 2 and 17 Hz, =CH_2), 5.11 (dd, 2H, *J* = 2 and 10 Hz, =CH_2), 4.11-4.07 (m, 2H, OCH), 1.54-1.47 (m, 4H, CH_2), 1.44-1.36 (m, 4H, CH_2), 0.92 (t, 6H, J = 7 Hz, CH_3). MS (ESI) *m/z* = 183.2 $[M+H]^+$.

Dihex-2-en-1-yl ether (11) and hex-2-en-1-yl hex-1-en-3-yl ether (12) (mixture of products). ^{1}H-NMR major component **11** ($CDCl_3$): δ 5.58-5.55 (m, 2H,=CH), 4.03 (d, 2H, *J* = 5 Hz, =OCH_2), 2.06-2.04 (m, 2H, CH_2); 1.43-1.36 (m, 4H, CH_2), 0.91 (t, 3H, *J* = 7 Hz). MS (ESI) *m/z* = 183.1 $[M+H]^+$.

Hex-1-en-3-yl *n*-octyl ether (13). ^{1}H NMR ($CDCl_3$): δ 5.60 (m, 1H, H-allyl), 5.09 (dd, 1H, *J* = 2 and 16 Hz, H_2C=), 5.07 (dd, 1H, *J* = 2 and 10 Hz, H_2C=), 3.57-3.53 (m, 1H, OCH); 3.42-3.39 (m, 1H, OCH), 3.18-3.15 (m, 1H, OCH), 1.51-1.22 (m, 16H, CH_2), 0.86-0.78 (m, 6H, CH_3). MS (ESI) *m/z* = 183.3 $[M+H]^+$.

Hex-2-en-1-yl *n*-octyl ether (14). ^{1}H NMR ($CDCl_3$): δ 5.61-5.56 (m, 2H,=CH), 4.00 (d, 2H, *J* = 5 Hz, =OCH_2), 3.43-3.38 (m, 2H, OCH_2); 2.10-2.06 (m, 2H, CH_2), 1.56-1.22 (m, 12H, CH_2), 0.90-0.71 (m, 6H, CH_3). MS (ESI) *m/z* = 183.3 $[M+H]^+$.

Phosphonium salt formation. 2.5 μmol of [$RuCpCl(PPh_3)_2$], 5 μmol of AgOTs, 0.05 mmol of triphenylphosphine and 0.05 mmol of HOTs were charged into the reaction vessel and flushed with argon. Degassed and dried toluene was added (2.5 ml) and the mixture was stirred for five minutes. Allylic alcohol **6** or **7** was added (5 mmol) and the reaction was stirred at 60 °C for one hour. Reaction was cooled to room temperature and the mixture was concentrated *in vacuo*. The phosphonium salts were washed with petroleum ether to yield a colorless oil (100% conversion of triphenylphosphine). The products were isolated with preparative HPLC.

Preparative HPLC method. Preperative HPLC was performed with a HPLC system consisting of a Dionex P580 pump (Dionex) connected with an UV-detector (Seperations) operating at 260 nm. The HPLC was carried out with an Alltima HP C18 5u reverse phase column (250x10 mm), with a flow of 4 ml/min and repetitive injection of 250 ul of a 10 mg/ml solution in acetonitrile. A binary gradient of acetonitrile (eluent A) and 0.1 M ammoniumacetate (eluent B) was used. The gradient conditions were at t = 0-20 (minutes) eluent A (%) / eluent B (%) = 50/50, t = 20-36 acetonitrile 100%, t = 36-55 eluent A (%) / eluent B (%) = 50 / 50.

Hex-1-en-3-yl triphenylphosphonium tosylate (15). ^{1}H-NMR ($CDCl_3$): δ 7.90-7.86 (m, 3H, ArH), 7.79-7.73 (m, 6H, ArH), 7.67-7.60 (m, 6H, ArH), 6.65 (ddd, 1H, *J* = 7, 24 and 30 Hz, H-allyl), 2.51-2.22 (m, 2H, H_2C=), 2.18-2.14 (m, 3H, PCH and CH_2), 2.02 (s, 3H, OTs), 1.15-1.11 (m, 2H, CH_2), 0.76 (t, 3H, J = 7 Hz, CH_3. $^{31}P\{^1H\}$-NMR ($CDCl_3$): δ 26.5 (s). MS (ESI) *m/z* = 345.4 $[M–OTs]^+$.

Hex-2-en-1-yl triphenylphosphonium tosylate (16). ^{1}H-NMR ($CDCl_3$): δ 7.83-7.75 (m, 7H, ArH), 7.73 (m, 8H, ArH), 5.72-5.64 (m, 2H, CH=), 4.11 (d, 2H, *J* = 5 Hz PCH_2), 2.34 (s, 3H, OTs), 2.03 (m, 2H, CH_2), 1.46-1.34 (m, 2H, CH_2), 0.88 (t, 3H, J = 7 Hz, CH_3). $^{31}P\{^1H\}$-NMR ($CDCl_3$): δ 21.6 (s). MS (ESI) *m/z* = 345.4 $[M–OTs]^+$.

Theoretical methods. The calculations were carried out using the Hartree-Fock method with the 6-31G(d,p) basis set. The SPARTAN '04 package (Wavefunction, Inc;

www.wavefun.com) was used to carry out the calculations. All the geometry optimizations were carried out using Pople's 6-31G* (d,p) for H, C and O atoms.[34] All of the geometrical parameters were fully optimized, and all of the structures located on the PESs were characterized as minima.

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6

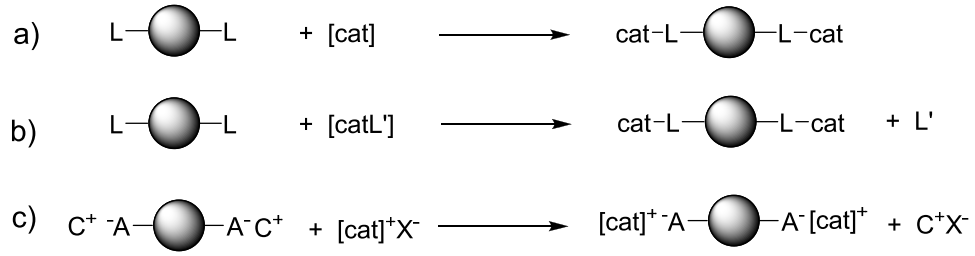
Immobilization of ruthenium catalysts for allylations with allyl alcohol as allylating agent

Abstract
$[RuCp(PP)]^+$ complexes active for allylation of alcohols with allyl alcohol as the allylating agent were immobilized on solid supports. Two different immobilization methods have been applied: (1) via electrostatic interactions of the cationic complex on ion-exchange resins, where the anion is present on the support, and (2) via a coordination bond with a ligand covalently bound on the support. Both methods give high yields of immobilized complex through relatively simple procedures. The catalysts immobilized via ionic interactions prove to be able to allylate both 1-octanol and 4-*tert*-butylphenol with very low leaching of the catalyst, thus forming allyl octyl ether and C-allylated phenol, respectively. The accumulation of water in the highly hydrophilic resin precludes the O-allylation of phenol and also retards the C-allylation reaction. The catalysts immobilized via a coordination bond are not hydrophilic; with these catalysts selective O-allylation of phenols is achieved, with recycling of the catalysts over multiple runs. Leaching of the catalyst from the support is somewhat higher than for the electrostatically-bound catalyst and quarternisation (allylation) of the excess of phosphine groups present on the support plays an important role in the activity of the immobilized catalysts for the allylation reaction.

6.1 Introduction

Several homogeneous catalysts are known to catalyze the reaction between an aliphatic or aromatic alcohol and allyl alcohol, all being precious metal-ion complexes. The successful ruthenium-based systems described in Chapter 2-5 only need catalyst amounts of 0.1 mol% on substrate or less and do not rely on the use of stoichiometric amounts of additives to control activity and selectivity; however, the catalytic system is present in the same phase as the substrates and products, from which it is difficult to recover after the reaction. It would be desirable to find a means of recycling of the catalyst, which may be achieved by immobilization of the active complex onto a non-soluble support. A simple filtration after the reaction could then be performed or the catalyst could thus be used in a continuous process by flushing the substrates through a fixed-bed.

Immobilization of homogeneous catalysts on solid supports is a well-studied field of research. Several methods can be used to attach a metal complex onto an insoluble support. One often applied method is to covalently link one of the ligands of the reactive complex onto the support. Typical supports are polystyrenes[1] and inorganic materials.[2] A complex with a free coordination site can be added to a resin with coordinating groups (Scheme 6.1a),[3] but a more common approach is the substitution of a ligand from the complex with a ligand present on the support (Scheme 6.1b).[4,5] The advantage of covalently-bound ligands is that the linkage between ligand and support is very stable, but a disadvantage is that a change of synthesis is required of at least one of the catalyst ligands and thus the complex, which can be cumbersome and expensive. It may also affect the catalyst's structure, which is undesirable as it may change the reactivity of the catalyst. These disadvantages can be overcome by immobilizing the catalyst using non-covalent interactions for which several methods are known, ranging from strongly ionic to weak Van der Waals interactions to confine the catalyst to a support.[6] Amongst the non-covalent interactions, the ionic interaction is the most



Scheme 6.1. Immobilization strategies: a) coordination of an unsaturated complex onto a support with a coordinating residue, b) coordination of a saturated complex onto a support via ligand substitution with a coordinating residue and c) absorption of a cationic complex onto an anionic ion-exchange support.

stable.[7-9] By adding a cationic catalyst to an anionic ion-exchange resin, an electrostatically-immobilized catalyst is obtained (Scheme 6.1c). Advantages of this method are that the immobilization process is often fairly easy and the active catalyst does not need to be modified. Furthermore, reloading of the support with fresh catalyst is readily achieved using this method. A disadvantage of this method is that it can only be applied for ionic catalysts, which have to keep their charge throughout the whole catalytic cycle in order to remain immobilized.

In this Chapter, the immobilization of a number of the catalysts described in Chapters 2–5 is demonstrated, and their application in heterogeneous allylation reactions is explored. The ionic as well as the covalent immobilization approach was used and the resulting heterogenized catalysts were tested in allylation reactions of aliphatic alcohols and phenols with allyl alcohol as the allyl donor.

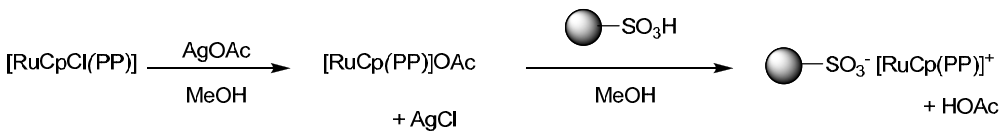
6.2 Results and discussion

6.2.1 Ionic immobilization of [RuCp(PP)]$^+$

Catalyst synthesis

TThe RuCp complexes with bidentate phosphine ligands previously used in allylation reactions required a non-coordinating anion in order to be catalytically active. The presence of a tosylate (*p*-toluenesulfonate) anion gives very active catalysts, but also other anions like triflate (trifluoromethanesulfonate) or PF_6^- can be used. Many commercially available ion-exchange resins carry tosylic and triflic acid-type residues, such as DOWEX 50 WX (tosylate), Amberlyst 15 (tosylate) and Nafion NR 50 (triflate). The polystyrene scaffold is expected to be very stable and unreactive under the reaction conditions described in the previous Chapters. Therefore these resins were chosen for immobilization. Other supports like silicates or aluminates contain hydroxyl residues and may therefore interfere in the desired allylation reactions.

The [RuCp(PP)Cl] complexes were synthesized following the procedure reported in the previous chapters. The chloride ion was then exchanged for an acetate anion, by reaction of



Scheme 6.2. Synthesis of cationic [RuCp(PP)]$^+$ complexes and immobilization on anionic-exchange resin.

Table 6.1. Efficiencies of loading of RuCp complexes on ion-exchange resins

entry	$[RuCp(PP)]^+$ PP =	resin	loading efficiency[a] (%)
1	dppe	DOWEX 50 WX 2	72
2	dppe	DOWEX 50 WX 4	85
3	dppe	DOWEX 50 WX 8	62
4	dppe	Amberlyst 15	79
5	dppe	Nafion NR 50	78
6	dppdep	DOWEX 50 WX 4	94
7	dppb	Nafion NR 50	98
8	$(PPh_3)_2$	Nafion NR 50	96

[a] amount of Ru-complex initially present in solution transferred onto the resin. 0.025 mmol of [RuCp(PP)](OAc) was added to 0.25 mmol H^+ on resin.

the complex with silver(I) acetate in methanol (Scheme 6.2). Methanol was used as a solvent, as it enhances swelling of the resin, making its reactive sites more accessible. The acidic ion-exchange resin was then added to the solution of the acetate complex.

The lower pKa of the acidic residues (< 1) on the resins compared to the pKa of acetic acid (~3.5) favors formation of the immobilized complex and acetic acid. A ratio acidic residues over Ru-complex of 10 was used, to ensure that enough accessible sites for the complex to bind were available; the presence of an excess of acidic residues was shown in the previous chapters to improve activity for allylation reactions. Different catalysts that are used to allylate both aliphatic alcohols and phenol were thus immobilized. An overview of the various immobilized catalysts thus prepared and the efficiency of loading of the various combinations is summarized in Table 6.1.

The precursor complex $[RuCp(dppe)]^+$ of the most active catalysts was immobilized on the commercially available DOWEX 50 WX resins. These are gel-type resins and different cross-linking percentages were employed (entries 1-3). Loading efficiencies were calculated by analysis of the Ru-content of the filtrate using ICP-AES (inductively coupled plasma atomic-emission spectroscopy) and were in the range of 70-85%. The Amberlyst 15 resin, also containing tosylic acid residues, but with a macroreticular structure, was used for comparison (entry 4). Loading was in the same range as for the DOWEX resins. Finally for $[RuCp(dppe)]^+$, the Nafion NR 50 resin, with triflic acid residues, was used as a support (entry 5). Again, immobilization proved to be successful and a high loading efficiency was achieved. For the other complexes, either DOWEX 50 WX 4 or Nafion NR 50 was used as the support, because with these resins the highest immobilization efficiencies were obtained (entries 6-8). Upon introduction of the resins to the ruthenium solutions the color of the solutions rapidly faded with the concurrent coloration of the resin (Figure 6.1a,b). For the Nafion NR 50 resin, the beads were homogeneously colored and when cut in half, the yellow

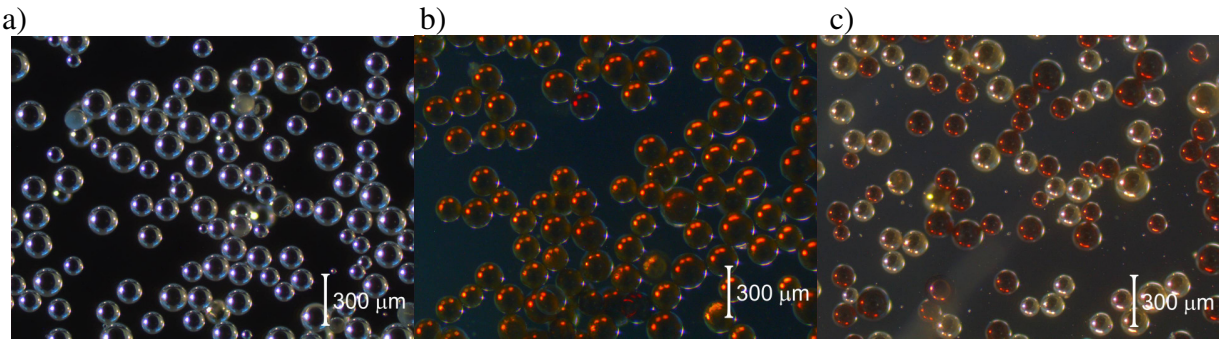


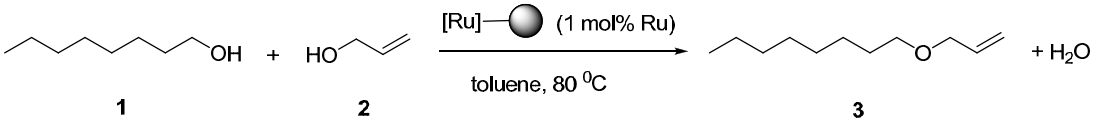
Figure 6.1. Pictures taken with an optical microscope equipped with a camera of: a) commercially available DOWEX 50 WX4 resin b) immobilized $[RuCp(dppe)]^+$ on DOWEX 50 WX4 resin and c) a mixture of newly introduced batch of resin to Ru-loaded resin.

color was also clearly present inside the bead, indicating penetration of the complex throughout the whole resin.

Interesting is the observation that when a second batch of resin was added to the loaded resin in solution and the mixture was stirred for several hours at room temperature, the complex did not migrate into the fresh resin (Figure 6.1c). Also at heating to reaction temperature (80 °C), migration was not observed. Also at reaction temperature (80 °C), migration was not observed. Despite the use of an excess of 10 equivalents of acidic sites with respect to the Ru-complex quantitative loadings were not achieved after 15 hours of reaction time, indicating that not all acidic sites present on the resin are accessible for the ruthenium complex to bind. An equilibrium reaction is not playing a role since increasing the amount of ruthenium complex in solution does not significantly increase the final loading.

Catalysis

The aliphatic alcohol 1-octanol was investigated for its reactivity in the allylation with allyl alcohol (Scheme 6.3). The catalyst of choice was immobilized $[RuCp(dppe)]^+$, as this proved to be a good catalyst in the homogeneous system described in Chapter 2. For $[RuCp(dppe)]^+$ on DOWEX 50 WX2 and DOWEX 50 WX4 (Table 6.1; entries 1-2), catalytic activity was observed; however, over multiple runs irreproducible results were obtained, possibly due to the loss of small amounts of the relatively small, powdery resin beads during the multiple Schlenk filtrations. The complex on DOWEX 50 WX8 resin (Table 6.1; entry 3) did not show



Scheme 6.3. Allylation of 1-octanol with allyl alcohol as allylating agent, in the presence of immobilized Ru-catalyst.

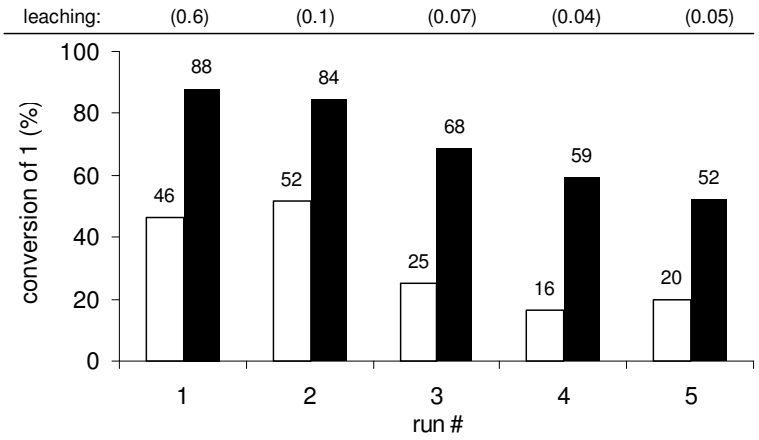
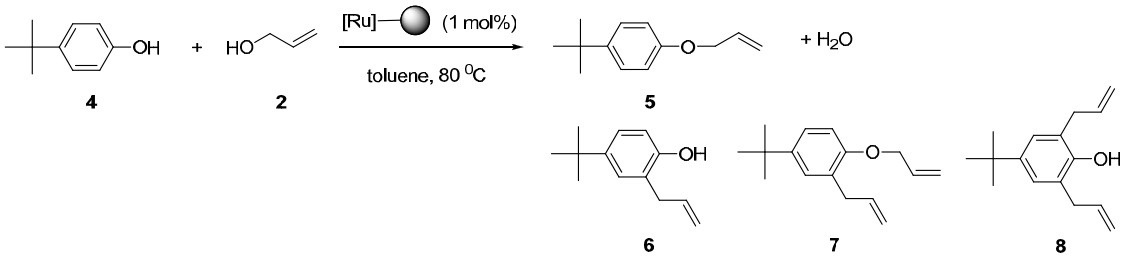


Figure 6.2. Allylation of 1-octanol with allyl alcohol using immobilized $[RuCp(dppe)]^+$ on Nafion NR 50 over multiple runs. Reaction conditions: ratio 1-octanol/allyl alcohol/Ru-complex = 100/200/1, toluene, 80 °C. 2.5 mmol of 1-octanol was used in each run. White bars represent conversion after 6 hours, black bars after 20 hours. Exact conversion numbers are indicated on top of the bars. Values in parentheses give percentage of Ru-complex leached from the resin relative to total Ru-complex present after 20 hours.

any activity in the allylation reaction. This is most likely caused by a limited substrate accessibility due to high cross-linking percentage of the polystyrene chains in this resin.

For the Nafion NR 50 support, no detectable loss of resin occurred, since this resin has large beads (10–35 mesh), unlike the DOWEX 50 WX resins. The results of the multiple catalytic reaction runs using $[RuCp(dppe)]^+$ on Nafion NR 50 are shown in Figure 6.2.

It was shown in the previous chapters that the use of an apolar solvent like toluene is essential to obtain a reasonable conversion in the allylation reaction. However, the use of such an apolar solvent is not beneficial for the swelling of the hydrophilic resins. Nonetheless, the allylation of 1-octanol with $[RuCp(dppe)]^+$ on Nafion NR 50 proceeded nicely with high yields and a very low level of leaching of the catalyst from the support. Over five consecutive runs, the conversions decreased significantly; however, this seems not to be caused by leaching of the catalyst, which is orders of magnitude lower than the decrease in conversion. The liquid reaction mixture which was separated by filtration from the immobilized catalyst did not show any activity in allylation reactions, indicating that the complex leached from the support is not causing activity during a reaction run. The decrease in activity could be caused by the retention of water in the resin due to the strongly hydrophilic sulfonate groups; during the multiple runs water thus accumulates in the resin, as a result shifting the reaction equilibrium towards the starting materials. When the beads are thoroughly warmed under vacuum (at 60 °C for 2 hours), loss of water is observed. A second explanation could be that chemical degradation of the catalyst occurs on the support without loss of its cationic nature, therefore staying immobilized.



Scheme 6.4. Allylation of 4-*tert*-butylphenol with allyl alcohol as allylating agent, in the presence of immobilized Ru-catalyst.

Also 4-*tert*-butylphenol was used as a substrate for the heterogeneously catalyzed allylation. Phenols can be O-allylated as well as C-allylated, thus forming several products (Scheme 6.4) and it was previously found that the structure of the catalyst plays a crucial role in determining the selectivity of this reaction. The results of the multiple reaction runs using $[RuCp(dppe)]^+$ immobilized on Nafion NR 50 as the catalyst are shown in Figure 6.3.

The reaction of 4-*tert*-butylphenol with allyl alcohol using the catalyst $[RuCp(dppe)]^+$ on Nafion resin proceeded again with relatively high conversion and low leaching. This catalytic system is completely selective for C-allylation; O-allylated product was not observed, not even at very short reaction times. Unlike in the allylation of 1-octanol, no significant deactivation was observed over multiple runs. C-allylation of phenols is thermodynamically favored over O-allylation and is an irreversible process. In contrast to O-allylation, the presence of water in the hydrophilic resin does not thermodynamically hinder the C-allylation reaction. However, the water environment inside the resin will change the local reaction medium and thus will certainly have its effect on the catalysis, for example by limiting

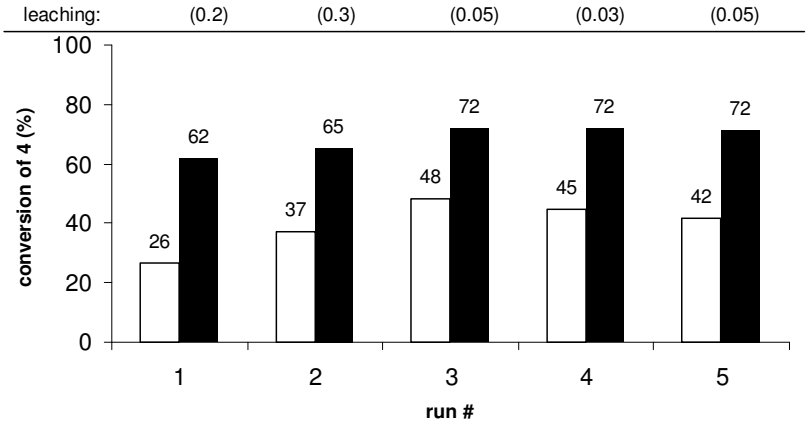


Figure 6.3. Allylation of 4-*tert*-butylphenol with allyl alcohol using immobilized $[RuCp(dppe)]^+$ on Nafion NR 50 over multiple runs. Reaction conditions: ratio 4-*tert*-butylphenol/allyl alcohol/Ru-complex = 100/200/1, toluene, 80 °C. White bars represent conversion after 6 hours, black bars after 20 hours. Only C-allylated products (**6**+**8**) are formed. Exact conversion numbers are indicated on top of the bars. Values in parentheses give percentage of Ru-complex leached from the resin relative to total Ru-complex after 20 hours.

Table 6.2. Allylation of 4-*tert*-butylphenol with allyl alcohol using immobilized $[RuCp(PP)]^+$ [a]

entry	$[RuCp(PP)]^+$ PP =	resin	conversion of **4** (%)		selectivity (%)[b]	
			6 h	20 h	**5**	**6-8**
1	dppdep	DOWEX 50 WX 4	4	11	37	63
2	dppb	Nafion NR 50	13	30	12	88
3	$(PPh_3)_2$	Nafion NR 50	1	2	100	0

[a] Reaction conditions: ratio 4-*tert*-butylphenol/allyl alcohol/Ru-complex = 100/200/1, toluene, 80 °C
[b] after 6 h.

conversion to about 72% after 20 hours. This water is also formed in the reaction of two molecules of allyl alcohol into diallyl ether, which also is an allylating agent, as was described previously. The hydrophobic diallyl ether will not be easily taken up in the hydrophilic resin, which limits its use as allyl donor.

In order to further investigate the possibilities for O-allylation, catalysts that were found to be highly selective for O-allylation were also immobilized onto the resin in a similar fashion (Table 6.1; entries 6-8) and tested for their activity in the allylation of 4-*tert*-butylphenol (Table 6.2). Unfortunately, the immobilized catalyst $[RuCp(dppdep)]^+$ is far less selective for O-allylation than the homogeneous counterpart, for which selectivities of 80% and higher were obtained at conversions below 50% (Chapter 3). The complexes $[RuCp(dppb)]^+$ (entry 2) and $[RuCp(PPh_3)_2]^+$ (entry 3), which have been shown to be very selective in the homogeneous allylation reaction (Chapter 2 and 4), show a very different catalytic behavior when immobilized onto an ion-exchange resin. The immobilized catalyst $[RuCp(dppb)]^+$ showed relatively high conversion of **4**, but selectivity for O-allylation was low. The immobilized catalyst $[RuCp(PPh_3)_2]^+$ showed very low activity, although the trace amount of product formed was the desired allyl phenyl ether. The fact that no propanal was formed indicates that the acidic residues on the support are available for catalysis and in this case clearly block the undesired allyl alcohol isomerization reaction. The different behavior of these catalysts when immobilized on ion-exchange resins is ascribed to the accumulation of water in the hydrophilic pores of the resin. Although seemingly the catalyst in Table 6.2, entry 3 is not active in the allylation of phenol, diallyl ether and thus water is formed in all cases. The O-allylation equilibrium therefore is shifted toward the starting material side, while the irreversible formation of C-allyl phenol is not hindered by the local high concentrations of water.

6.2.2 Coordinative immobilization of [RuCp(PP)]$^+$

Catalyst synthesis

In order to avoid the hydrophilic character of the anionic-exchange resins, another type of linkage between the catalyst and the support was investigated; a coordinative interaction between a covalently-bound phosphine at the support and a Ru complex is used. Such an immobilization should not change the structure of the catalyst too much, as large changes in the coordination sphere of the metal ion may have a dramatic effect on the catalytic behavior of the ruthenium complex, as was already shown for the homogeneous systems (Chapter 2-4). Therefore a covalently immobilized triphenylphosphine analogue (resinPhPPh$_2$) on a polystyrene backbone (Merrifield-type) was chosen as the solid support.[10] The use of monodentate phosphine ligands on ruthenium, together with an acidic promoter, has been shown to create a very active catalyst with high selectivity for the desired O-allylated phenol (Chapter 4).

The resin used has 3 milliequivalent (meq) phosphine groups per gram of resin, supported on a polystyrene resin with 2% divinylbenzenepolystyrene cross-linking. In solid state ^{31}P-NMR,

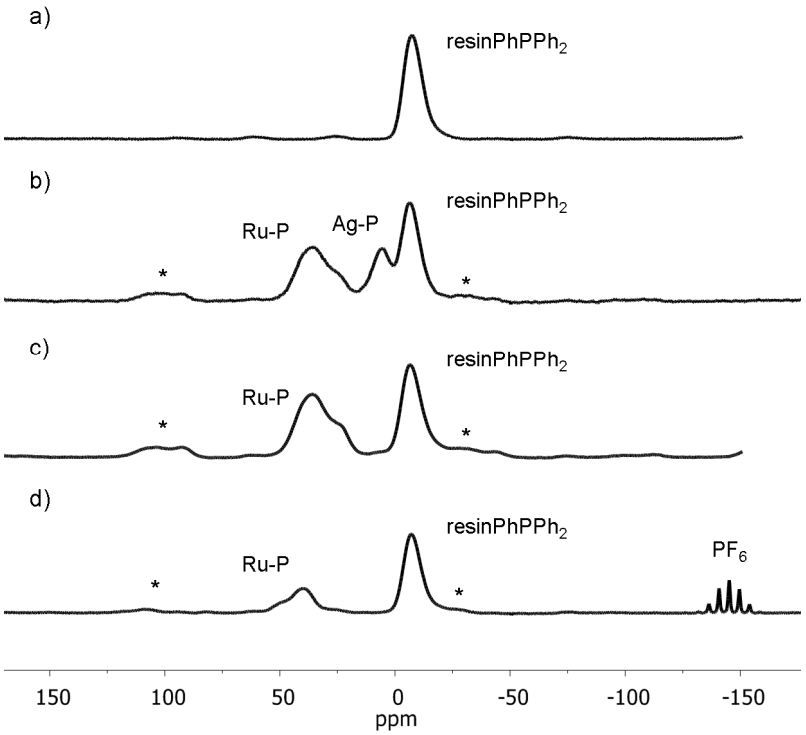
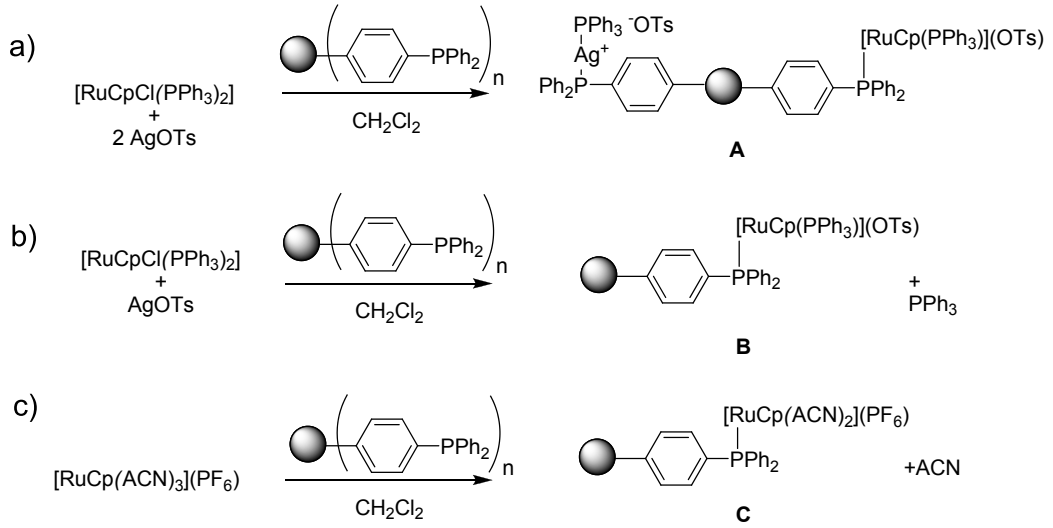


Figure 6.4. CP MAS ^{31}P-NMR spectra of a) resinPhPPh$_2$ b) AgPPh$_3$/RuCp(PPh$_3$)$_2$(resinPhPPh$_2$)](OTs) (catalyst **A**) c) RuCp(PPh$_3$)$_2$(resinPhPPh$_2$)](OTs) (catalyst **B**) and d) [RuCp(ACN)(resin-PhPPh$_2$)](PF$_6$) (catalyst **C**). Signals originating from the excess of free resin-bound phosphine are marked resinPhPPh$_2$, whereas those originating from Ru-coordinated phosphines are marked Ru-P and Ag-coordinated phosphines Ag-P. Signals originating from spinning side-bands are denoted *.

a single resonance is clearly observed (Figure 6.4a). An excess of 4 equivalents of resinPhPPh$_2$ was used with respect to the Ru-complex. [RuCp(PPh$_3$)$_2$](OTs), synthesized from [RuCpCl(PPh$_3$)$_2$] and 2 equivalents of AgOTs, was reacted with resinPhPPh$_2$ in the non-coordinating solvent dichloromethane. After stirring for 48 hours, the solution was almost completely colorless and the resin had obtained a yellow color. The efficiency of the loading was determined again with ICP-AES of the filtrate and it was found that 91% of the complex was transferred from solution onto the resin. The catalyst on resin, however, may consist of various species, depending on the extend of substitution of the triphenylphosphine ligands. After stirring for 48 hours at room temperature, ^{31}P-NMR of the filtrate did not show a signal corresponding to free triphenylphosphine, not even when the immobilized resin was washed thoroughly with dichloromethane by means of Soxhlet extraction. Solid state ^{31}P-NMR of the loaded resin (Figure 6.4b) indicates the presence of multiple phosphine-containing species: the free phosphine on resin (resinPhPPh$_2$) at –6.3 ppm (also present in Figure 6.4a), Ru-coordinated phosphine at +36.6 ppm, and a P species with a resonance at +5.2 ppm (Figure 6.4b). The latter resonance is assigned to a silver-phosphine species, that is present due to the excess of AgOTs used in the dehalogenation step (Scheme 6.5a).

It was confirmed that triphenylphosphine coordinated to Ag(I)(OTs) in solution indeed shows a resonance around +5 ppm. The fact that no free triphenylphosphine liberated from the Ru-complex was found in the filtrate is thus most likely caused by the coordination of the released phosphine ligand onto the Ag^+ ion. Indeed, when [RuCpCl(PPh$_3$)$_2$] is reacted with one equivalent of AgOTs and the resulting mixture is added to the resin after filtration, the



Scheme 6.5. Synthesis of a) immobilized [RuCpCl(PPh$_3$)$_2$] + 2 AgOTs on resin-bound triphenylphoshine (catalyst **A**), b) immobilized [RuCpCl(PPh$_3$)$_2$] + 1 AgOTs on resin-bound triphenylphoshine (catalyst **B**) and c) immobilized [RuCp(ACN)$_3$](PF$_6$) on resin-bound triphenylphosphine (catalyst **C**).

peak at +5.2 ppm is not present (Figure 6.4c; Scheme 6.5b) and the filtrate was shown to contain free triphenylphosphine.

The complex $[RuCp(ACN)_3](PF_6)$ (ACN = acetonitrile) was also immobilized onto the resin-bound phosphine (Scheme 6.5c). This precursor compound is a starting material often employed for the synthesis of various Ru(II)Cp-complexes and its coordination behavior has been widely studied.[11] Since it is known that phosphines easily displace an acetonitrile ligand from this ruthenium complex,[12] this compound was added to $resinPhPPh_2$ in dichloromethane. Indeed immediate coordination to the resin took place and a complex with the proposed formulation $[RuCp(ACN)(resinPhPPh_2)_2](PF_6)$ was obtained. From the initial amount of Ru-complex present in solution, 99% was loaded onto the resin. This newly obtained immobilized catalyst was analyzed by solid state ^{31}P-NMR (Figure 6.4d) and it was clearly observed that the $resinPhPPh_2$ was coordinated to ruthenium. Also the presence of the PF_6 anion is clearly indicated by the NMR spectrum. Most likely two $resinPhPPh_2$ moieties are coordinated to the ruthenium center, since it has been reported that displacement of two acetonitrile ligands with two phosphine ligands readily occurs at room temperature.[12]

The complexes thus immobilized are air stable when properly dried and can be used after several weeks without a significant decrease in activity.

Catalysis

The catalytic activity of catalyst **A** was investigated in the allylation of 1-octanol with allyl alcohol (Figure 6.5).

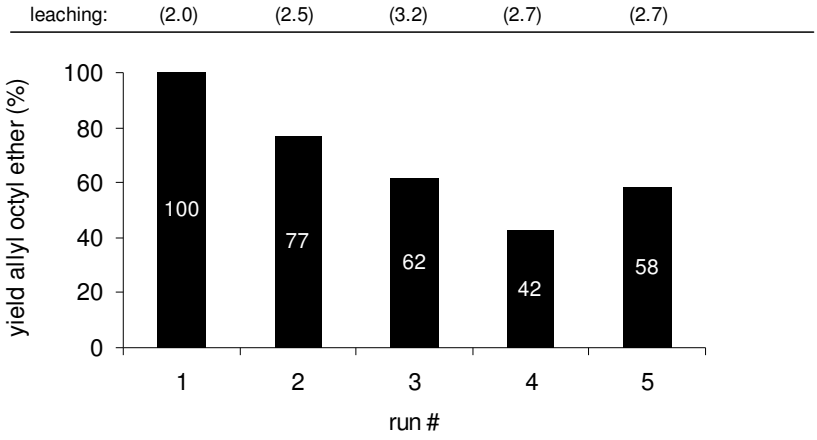


Figure 6.5. Allylation of 1-octanol with allyl alcohol using immobilized $[RuCp(PPh_3)_2](OTs)$ (catalyst **A**) on resin-bound triphenylphosphine over multiple runs. Reaction conditions: ratio 1-octanol/**2**/[Ru]/HOTs = 100/200/1/2; toluene; 80°C, 60 minutes; Exact conversion number indicated on top of bar. Values in parentheses give percentage of [Ru] leached from the resin after 60 minutes.

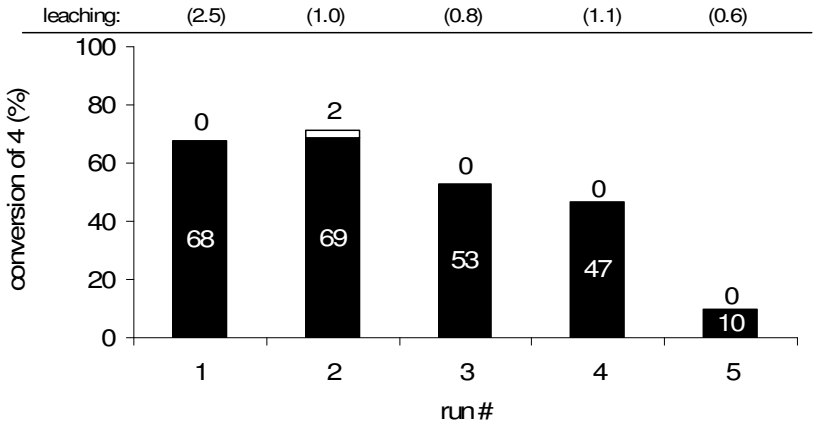


Figure 6.6. Allylation of 4-*tert*-butylphenol with allyl alcohol using immobilized $[RuCp(PPh_3)_2]^+$ (catalyst **A**) over multiple runs. Reaction conditions: ratio 4-*tert*-butylphenol **/2/**[Ru]/HOTs = 100/200/1/2; toluene; 80°C, 3 hours; yield of O-allylated product (**5**) represented by black bar, with exact number in white; yield of C-allylated products (**6-8**) represented by the white bar, with exact number in black. Values in parentheses give percentage of [Ru] leached from the resin after 3 hours.

The homogeneous catalyst $[RuCp(PPh_3)_2]^+$ was previously demonstrated to be only active for allylation in the presence of strong acid (Chapter 4). For the catalysts immobilized on ion-exchange resins described in section 6.2.1, the acid required for catalytic activity was present on the support, but in this case external acid HOTs is needed to be added and was therefore present in solution. Catalyst **A** showed a very high activity in the first run of the allylation of 1-octanol. The substrate was fully converted within 60 minutes into allyl octyl ether. In the following runs the conversion after 60 minutes was significantly lower, while the amount of complex leached from the support was constant. It must be noted that these conversions after 60 minutes were obtained with a catalyst loading much higher than that used in the homogeneous system (1.0 mol% vs 0.1 mol% on octanol for the homogenous catalysts) (Chapter 5). Leaching of ruthenium was considerably higher than for the catalysts immobilized using electrostatic interactions. This is indicative for a lower stability of a coordination bond compared to the electrostatic interaction. The liquid phase reaction mixture containing the complex leached from the support was separately tested for catalytic activity, but showed no conversion of added 1-octanol and this proved that the allylation activity is really due to the heterogeneous catalyst.

The challenge is of course, to perform selective O-allylation of phenol and therefore the allylation of 4-*tert*-butylphenol was performed using catalyst **A;** the results are shown in Figure 6.6.

While the catalysts immobilized on ion-exchange resin formed predominantly C-allylated product, this coordinatively-bound catalyst selectively forms O-allylated product; only traces of C-allylated products were observed. After three hours, conversions approaching 70% were

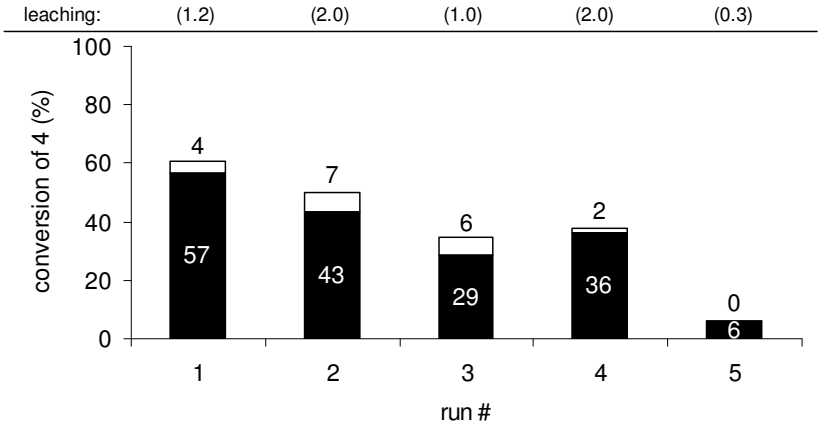


Figure 6.7. Allylation of 4-*tert*-butylphenol with allyl alcohol using immobilized $[RuCp(PPh_3)_2]^+$ (catalyst **A**) over multiple runs. Reaction conditions: ratio 4-*tert*-butylphenol /**2**/[Ru]/HOTs = 100/200/1/2; toluene; 60°C, 20 hours; yield of O-allylated product (**5**) represented by black bar, with exact number in white; yield of C-allylated product (**6-8**) represented by the white bar, with exact number in black. Values in parentheses give percentage of [Ru] leached from the resin after 20 hours.

reached. It must again be noted that similar conversions were obtained after three hours with the homogeneous system (Chapter 4) with the difference that a much higher catalyst loading was used here and a higher temperature is used (80 °C vs 60 °C for the homogeneous system). Thus the heterogeneous system is significantly less active, which is most likely caused by diffusion limitations of the substrates into the solid support.

The conversion gradually decreased over the first consecutive four runs; in the fifth run only 10% of phenol was converted. The amount of leached complex does not account for this rapid decrease and therefore a change or chemical deactivation of the complex present on the support must occur. The reaction was also performed at 60 °C in order to investigate whether this rapid decrease of activity could be prevented by lowering the reaction temperature (Figure 6.7).

The activity of catalyst **A** at 60 °C is of course lower than at 80 °C and therefore the reaction was run for 20 hours; again, a high selectivity for O-allylation was observed. Intriguingly, the fifth consecutive run shows again a large decrease in conversion; apparently deactivation of the catalyst is also taking place at this reaction temperature.

Catalyst **B** was also tested as catalyst for the allylation of phenol and the results over five subsequent runs are shown in Figure 6.8. The large difference between the first and second run can be explained by the consumption of the acid added to the reaction. Phosphines (here immobilized) react with allyl alcohol and strong acid into allyl phosphonium salts and water, but only in the presence of an allylation catalyst, as described in Chapter 4. Due to consumption of the acid, apart from the allyl phenyl ether, propanal is also formed by isomerization of allyl alcohol. The immobilized allylphosphonium groups are observed in

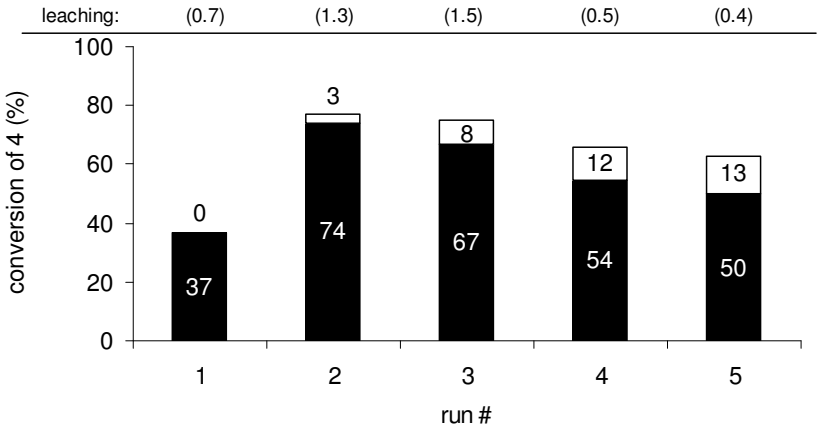


Figure 6.8. Allylation of 4-*tert*-butylphenol with allyl alcohol using immobilized $[RuCp(PPh_3)_2]^+$ (catalyst **B**) over multiple runs. Reaction conditions: ratio 4-*tert*-butylphenol /**2**/[Ru]/HOTs = 100/200/1/2; toluene; 80°C, 3 hours; yield of O-allylated product (**5**) represented by black bar, with exact number in white; yield of C-allylated products (**6**-**8**) represented by the white bar, with exact number in black. Values in parentheses give percentage of [Ru] leached from the resin after 3 hours.

solid state ^{31}P-NMR (Figure 6.9), where the resonance at –6.3 ppm from the resinPhPPh$_2$ (Figure 6.9a) has disappeared with the appearance of a resonance at 19.7 ppm assigned to the allyl phosphonium species (Figure 6.9b).

In the second run with catalyst **B**, when the free resinPhPPh$_2$ moieties have been totally converted into phosphonium species, the acid co-catalyst (HOTs) is not consumed, thus

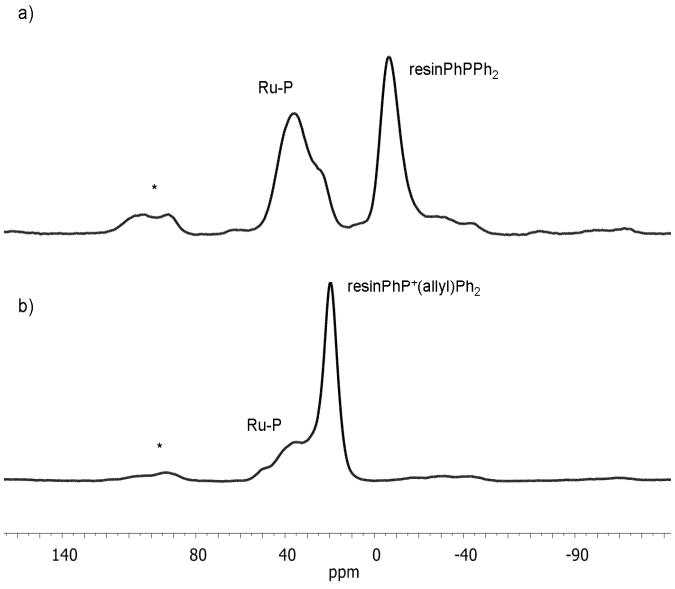


Figure 6.9. CP MAS ^{31}P-NMR spectra of a) $RuCp(PPh_3)_2(resinPhPPh_2)](OTs)$ (catalyst **B**) and b) catalyst **B** after first run in allylation of 4-*tert*-butylphenol with allyl alcohol. Signals originating from the excess of free resin-bound phosphine are marked resinPhPPh$_2$, whereas those originating from Ru-coordinated phosphines are marked Ru-P and those originating from allyl phosphonium salts resinPhP$^+$(allyl)Ph$_2$. Signals originating from spinning side-bands are denoted *.

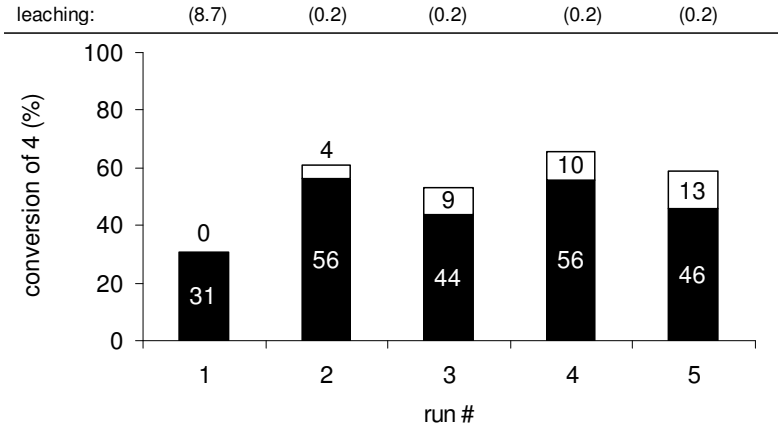
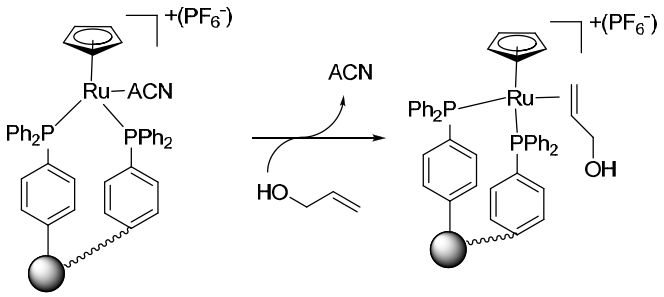


Figure 6.10. Allylation of 4-*tert*-butylphenol with allyl alcohol using immobilized $[RuCp(ACN)_3](PF_6)$ (catalyst **C**) on resin-bound triphenylphosphine over multiple runs. Reaction conditions: ratio 4-*tert*-butylphenol /**2**/[Ru]/HOTs = 100/200/1/2; toluene; 80°C, 3 hours; yield of O-allylated product (**5**) represented by black bar, with exact number in white; yield of C-allylated product (**6-8**) represented by the white bar, with exact number in black. Values in parentheses give percentage of Ru-complex leached from the resin after 3 hours.

making the catalyst active for O-allylation. In the following runs, conversions and selectivities towards O-allylation slowly decreased, but the catalyst **B** appeared to be more stable than catalyst **A**. The fact that catalyst **A** shows a much higher conversion in the first run is most likely caused by the coordination of the silver(I)tosylate to the resin$PhPPh_2$ moiety, making them inaccessible for quarterisation and preventing acid consumption. This hypothesis is supported by the observation that propanal is not formed in the first run when catalyst **A** is used.

When catalyst **C** was used as a catalyst in the reaction between 4-*tert*-butylphenol and allyl alcohol in the presence of acid (Figure 6.10), in the first run only 35% of allyl phenyl ether was obtained and propanal was formed, again indicative of the consumption of acid and quarternisation of the remaining free phosphines. The remaining molecule of acetonitrile is not playing a role during the catalysis, since it is most likely replaced by the large excess of substrate allyl alcohol present during the reaction (Scheme 6.6), creating an almost identical



Scheme 6.6. Substitution of an ACN ligand from $[RuCp(resin\text{-}PhPPh_2)_2(ACN)](PF_6)$ with allyl alcohol.

complex as described earlier with two coordinated triphenylphosphine ligands and a non-coordinating anion. The amount of ruthenium leached from the support is high in the first run, but rather low in the following runs. Conversions of phenol after 3 hours are relatively stable over multiple runs and the selectivity is similar to that in the reactions with catalyst **B.**

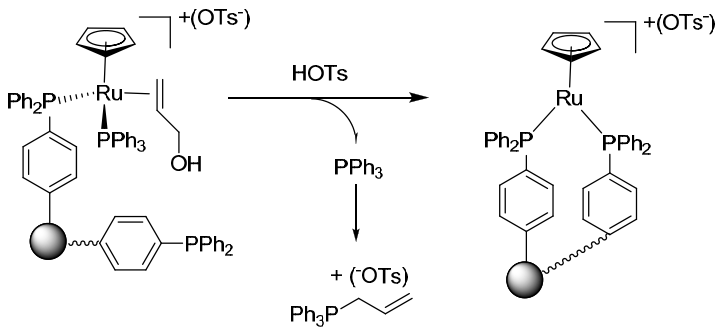
Chemical deactivation of the catalysts

Analysis with ^{31}P-NMR of the filtrate after the first run in the series with catalysts **A**, **B** and **C** shows the presence of phosphonium salts, indicating that free triphenylphosphine was present during the reactions, which is rapidly converted by the catalyst into allyl phosphonium salts (Scheme 6.7) as described in Chapter 4. When a triphenylphosphine ligand is released, its place will be taken by an immobilized phosphine group (Scheme 6.7). However, the immobilized phosphines also form immobilized phosphonium salts as indicated by the NMR spectra in Figure 6.9.

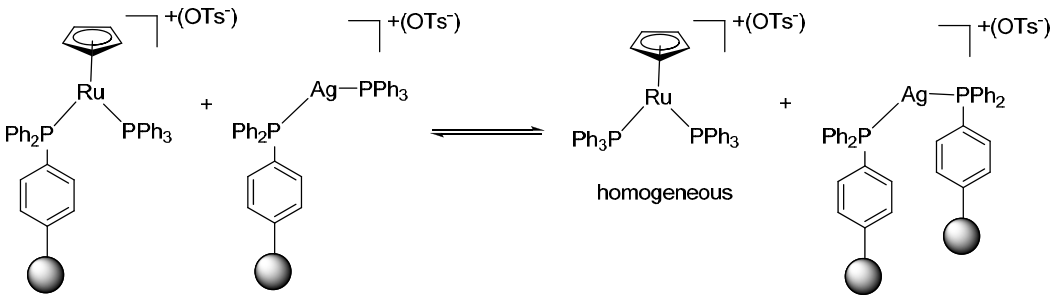
Coordinated phosphines are not prone to allylation; however, when the concentration of the substrate decreases, it is expected that some quarternization of coordinated phosphines occurs, thus causing deactivation of the catalyst.

Physical deactivation of the catalysts

After each run the reaction mixture was cooled to room temperature, filtered and the residual resin was washed with dichloromethane. Leaching of ruthenium was determined by quantifying the amount of Ru present in the combined filtrates after each reaction run. For catalyst **A**, it appeared that the leaching is considerably higher when the reaction mixture was filtered while still hot (8.4% vs 2.5% in a single run). This indicates that when the immobilized catalyst is heated to reaction temperature, it dissociates from the support and can be active as if it were a homogenous catalyst. The equilibrium reaction shown in Scheme 6.8 determines the amount of homogeneous complex present in solution. Most likely, the



Scheme 6.7. Proposed substitution of triphenylphosphine with resin-bound triphenylphosphine.



Scheme 6.8. Proposed mechanism for conversion of heterogeneous Ru-complex to homogeneous Ru-complex.

triphenylphosphine ligand still present on the silver ions plays a crucial role to facilitate this process, because for the catalysts **B** and **C** such a difference in the amount of leached Ru is not observed and leaching of ruthenium at reaction temperature is similar to that at room temperature. Also, after the first run a difference between cold and warm filtration is not present anymore for catalyst **A**, probably because the excess of phosphine is converted to allyl phosphonium salt. The extra equivalent of PPh_3 induces this difference in leaching, because at higher temperatures, the weakly coordinated PPh_3 on silver(I) dissociates, migrates to a Ru-species, and displaces a resin$PhPPh_2$ group, thus resulting in a homogeneous complex. At room temperature, the Ag-PPh_3 complex is more stable and the PPh_3 ligand present on Ru can migrate back to the silver ion present on the resin.

Such a "boomerang" effect, where the catalyst dissociates from the support during the reaction and returns after the reaction is finished (in our case when the reaction is cooled down) has been reported earlier for other catalytic systems.[13,14] The advantage of such a system is that the catalyst is homogeneous during the reaction and thus shows a high activity and selectivity. After the reaction, the catalyst becomes heterogeneous again and is easily separated from the reaction mixture. A disadvantage is that the amount of complex leached is significantly higher than for a fully heterogeneous system.

6.3 Conclusions

The use of ion-exchange resins as support has been shown to yield stable immobilized cationic Ru-complexes with which catalytic allylation reactions were successfully performed. Due to the hydrophilicity of these resins, however, water is retained in the resin, which is detrimental for the selective O-allylation of phenol. The retention of water in the resin causes the formation of only C-allylated products in the catalytic allylation of phenol. The immobilization of the ruthenium catalysts by covalently bound phosphine onto supports without hydrophilic residues makes O-allylation possible. Although leaching from the resin is

considerably higher than for the catalyst immobilized on ion-exchange resins, the activity over multiple runs is relatively stable. The activity of all heterogeneous systems described in this paper is significantly lower than that of the homogenous catalysts described in the previous chapters.

6.4 Experimental

General. All manipulations were performed under an argon atmosphere using standard Schlenk techniques. Solvents were dried and distilled by standard procedures and stored under argon. DOWEX 50 WX 4 (1.1 meq H^+/ml), Amberlyst (4.7 meq H^+/g) and Nafion (0.8 meq H^+/g) ion-exchange resins were purchased from Sigma-Aldrich. Resin-bound triphenylphosphine (resinPhPPh_2) (3 meq phosphine residue/g; 2% DVB/polystyrene) and [RuCp$(ACN)_3$]PF_6 were commercially available and used as received.
[RuCpCl$(PPh_3)_2$],[15] [RuCpCl(dppe)],[16] and [RuCpCl(dppb)],[17] were prepared according to literature procedures. The synthesis of [RuCpCl(dppdep)] is described in Chapter 3. The products of the allylation reactions are described in previous Chapters. Loading and leaching of the ruthenium complexes was quantified by determination of the Ru-content of the filtrates with a Varian-MPX CCD simultaneous ICP-AES. Pictures of resin were taken with a Zeiss Axiovert 125M microscope equipped with a colorview camera. Solid-state CP MAS ^{31}P-NMR spectra were recorded on a Bruker MSL 400 spectrometer operating at 161.99 MHz with a rotational spin speed of 11 kHz.

General procedure for the immobilization of complexes on ion-exchange resins. 0.025 mmol of [RuCp(PP)Cl] and 0.05 mmol of AgOAc were charged into a reaction vessel which was flushed with argon. Degassed methanol was added (5 ml) and the mixture was refluxed for one hour. After cooling to room temperature, Celite (200 mg) was added, and the suspension was filtered under argon. The residue was washed with methanol (3 × 2 ml) and to the combined filtrate, the resin (0.25 mmol H^+ residues) was added. This mixture was stirred (100 rpm) for 15 hours at room temperature. Finally the yellow beads were collected by filtration and washed with methanol (3 × 2 ml). The efficiency of the loadings was estimated by means of measuring the Ru-content in the combined filtrates with ICP-AES.

Immobilization of [RuCp$(PPh_3)_2$](OTs) onto resin-bound triphenylphosphine (catalyst A). [RuCpCl$(PPh_3)_2$] (72 mg; 0.1 mmol) was reacted with AgOTs (50 mg; 0.2 mmol) by refluxing in dichloromethane (5 ml) for 10 minutes. The reaction mixture was then filtered under argon over Celite and to the filtrate was added the resin-bound triphenylphosphine (135 mg; 0.4 mmol phosphine residues) and stirred (100 rpm) at room temperature for 48 hours. The resin was collected and washed with dichloromethane (3 × 4 ml). The efficiency of the loading was measured in duplicate by means of measuring the Ru-content in the combined filtrates with ICP-AES to find that 91% of the initial Ru-complex was present on the support.

Immobilization of [RuCp$(PPh_3)_2$](OTs) onto resin-bound triphenylphosphine (catalyst B). [RuCpCl$(PPh_3)_2$] (72 mg; 0.1 mmol) was reacted with AgOTs (25 mg; 0.1 mmol) by refluxing in dichloromethane (5 ml) for 10 minutes. The reaction mixture was then filtered under argon over Celite and to the filtrate was added the resin-bound triphenylphosphine (135 mg; 0.4 mmol phosphine residues) and stirred (100 rpm) at room temperature for 48 hours. The resin was collected and washed with dichloromethane (3 × 4 ml). The efficiency of the

loading was measured in duplicate by means of measuring the Ru-content in the combined filtrates with ICP-AES to find that 97% of the Ru-complex was present on the support.

Immobilization of $[RuCp(ACN)_3](PF_6)$ onto resin-bound triphenylphosphine (catalyst C). $[RuCp(ACN)_3](PF_6)$ (44 mg, 0.1 mmol) was dissolved in dichloromethane (5 ml) and resin-bound triphenylphosphine was added 133 mg, 0.4 mmol phosphine residues). The resulting suspension was stirred (100 rpm) for one hour, after which the solid was collected by filtration, washed with dichloromethane (3 × 2 ml) and dried *in vacuo*. The efficiency of the loading was measured in duplicate by means of measuring the Ru-content in the combined filtrates with ICP-AES to find that 99% of the initial Ru-complex was present on the support.

General procedure for catalytic reactions using catalyst immobilized on ion-exchange resins. To the immobilized complex (0.025 mmol) under argon atmosphere, 2.5 mmol of 1-octanol or 4-*tert*-butylphenol was added. Degassed and dried toluene was added (4 ml) and the mixture was stirred for five minutes. Allyl alcohol was then added (5 mmol) and the reaction was stirred (100 rpm) for 20 hours at 80 °C. Samples were taken at certain time intervals with an airtight syringe and analyzed by gas chromatography. After the reaction, the solid was collected by filtration, washed with methanol (3 × 2 ml) and dried *in vacuo*. Leaching amounts were measured in duplicate by means of measuring the Ru-content in the combined filtrates with ICP-AES.

General procedure for catalytic reactions using catalyst immobilized on resin-bound triphenylphosphine. To the immobilized complex (0.025 mmol) under argon atmosphere, 2.5 mmol of 1-octanol or 4-*tert*-butylphenol and 0.05 mmol of *p*-toluenesulfonic acid were added. Degassed and dried toluene was added (4 ml) and the mixture was stirred for five minutes. Allyl alcohol was added (5 mmol) and the reaction was stirred (100 rpm) for 3 hours at 80 °C or 20 hours at 60 °C. Samples were taken at certain time intervals with an airtight syringe and analyzed by gas chromatography. After the reaction, the solid was collected by filtration, washed with dichloromethane (3 × 2 ml) and dried *in vacuo*. Leaching amounts were measured in duplicate by means of measuring the Ru-content in the combined filtrates with ICP-AES.

GLC method. Quantitative gas liquid chromatography analyses were carried out on a Varian CP-3800 apparatus equipped with a VF-1ms (25 m × 0.25 mm) column with decane as internal standard. The temperature gradient used was: isothermal for 5 minutes at 40 °C, heating 10 °C/ minute to 250 °C and finally isothermal for 5 minutes at 250 °C.

6.5 References

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7

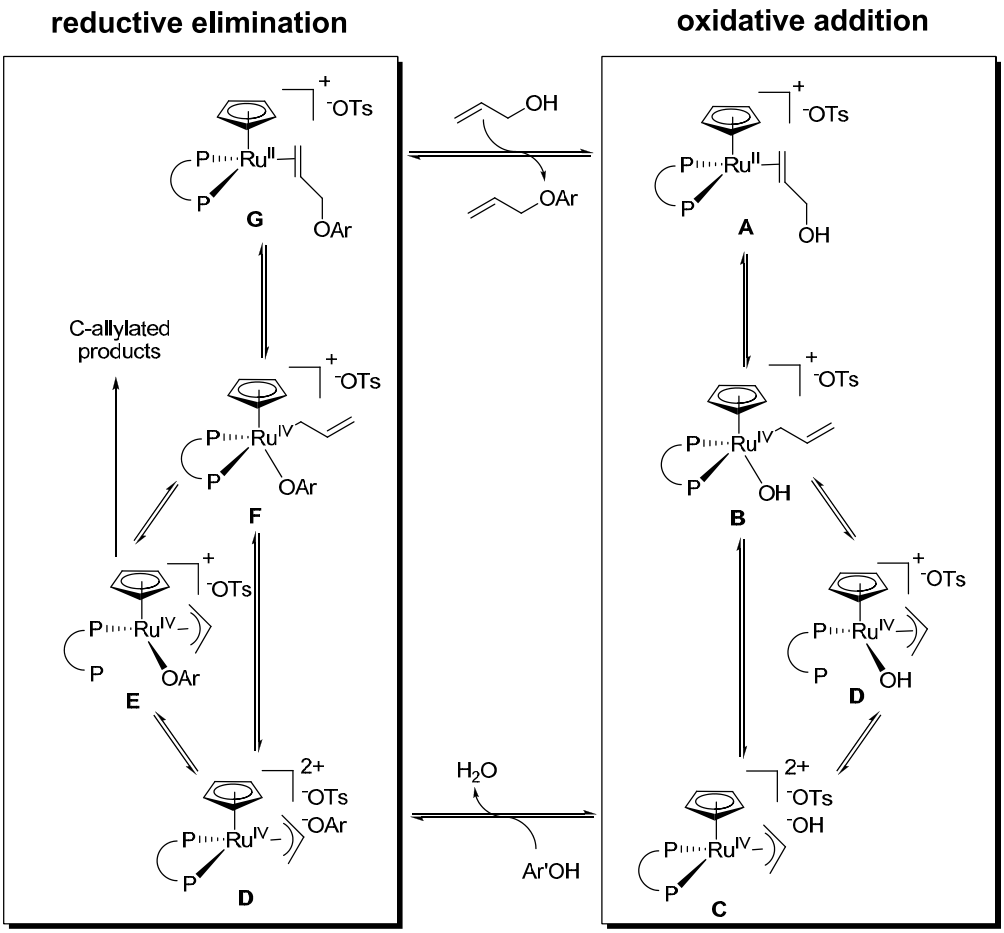
Theoretical study on the mechanism of $[RuCp(PP)]^+$-catalyzed allylation of phenol with allyl alcohol

Abstract
The two steps in the mechanism of catalytic allylation reaction determining activity and selectivity are an oxidative addition and reductive elimination, respectively. The intermediates, proposed in the previous chapters to play a key role in these steps, have been modelled using Density Functional Theory. The relative energies of the intermediates as a function of the phosphine ligand present on the ruthenium centre are discussed and the results nicely illustrate the role of the ligand in the stabilization of certain intermediates. Calculations were made for the situation in the absence as well as in the presence of acid. Several observations made from experiments in previous chapters are reflected in the energy calculations. In some instances entropic effects must also play a significant role. However, the DFT computational method used does not take entropy into consideration.

7.1 Introduction

In the previous chapters, the performance of cationic $[Ru(II)Cp(PP)]^+$ complexes as catalysts for the O- and C-allylation of phenols with allyl alcohol is discussed. Both the activity and selectivity in the catalytic allylation of phenols strongly depend on the structural characteristics of the complexes, and in particular on those of the bidentate phosphine ligands. It appeared that initially formed O-allylated products can be consecutively converted into C-allylated phenolic products, but the rate of this reaction also strongly depends on the structure of the catalyst. Addition of catalytic quantities of strong acid to the catalyst system not only leads to increased activity in the allylation reaction, but also affects the selectivity of the reaction.

Most of the publications on ruthenium-catalyzed allylation do not address the precise mechanism of either O- or C-allylation.[1-4] Often the role of the ligands is overlooked, whereas it was shown in the previous chapters to be crucial for both activity and selectivity.



Scheme 7.1. Proposed catalytic cycle for allylation of phenols with allyl alcohol in the presence of $[RuCp(PP)]^+$ catalysts.

Furthermore σ- to π-allyl isomerization, a known process for these reactions,[5] is often not discussed and only the supposedly more stable π-allyl species are described. It has been suggested that for both O- as well as C-allylation the nucleophile attacks the coordinated π-allyl group from outside the coordination sphere.[2,4] However, with the Ru-diphosphine complexes described in this thesis, it is impossible to consistently relate outside nucleophilic attack on the π-allyl moiety of these complexes with the experimentally observed effects of, in many cases subtle, structural variations of the diphosphine ligands on these complexes' catalytic activity and selectivity in phenol allylation.

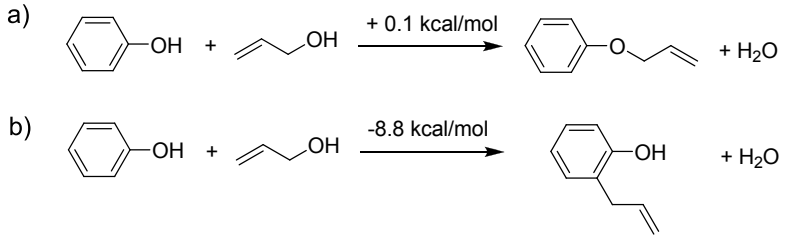
In this chapter, a more detailed study is described on the proposed mechanism of the ruthenium catalyzed O- and C-allylation of phenol (Scheme 7.1) as a function of the ligand structure of the catalyst. Possible intermediates are discussed and compared by means of DFT calculations, in particular those involved in the oxidative addition, which are related to the activity, and those of the reductive elimination, which determine the selectivity to the final product. Although several papers have reported calculations on allylation reactions,[6-8] none of these address the strong effects of the bidentate phosphine ligand on the rate and selectivity of these reactions.

7.2 Results and discussion

7.2.1 Overall reaction energies

In order to obtain a better insight in the thermodynamics of the two major reactions taking place in the catalytic allylation of phenol (Scheme 7.2), the overall reaction energies were first determined using DFT molecular calculations.

The formation of phenyl allyl ether (Scheme 7.2a) has an ΔE of +0.1 kcal/mol, while the formation of *ortho*-allylphenol has an ΔE of –8.8 kcal/mol (Scheme 7.2b). The C-allylated product therefore is the thermodynamic end-product of allylation, while the O-allylated product is a kinetic product.

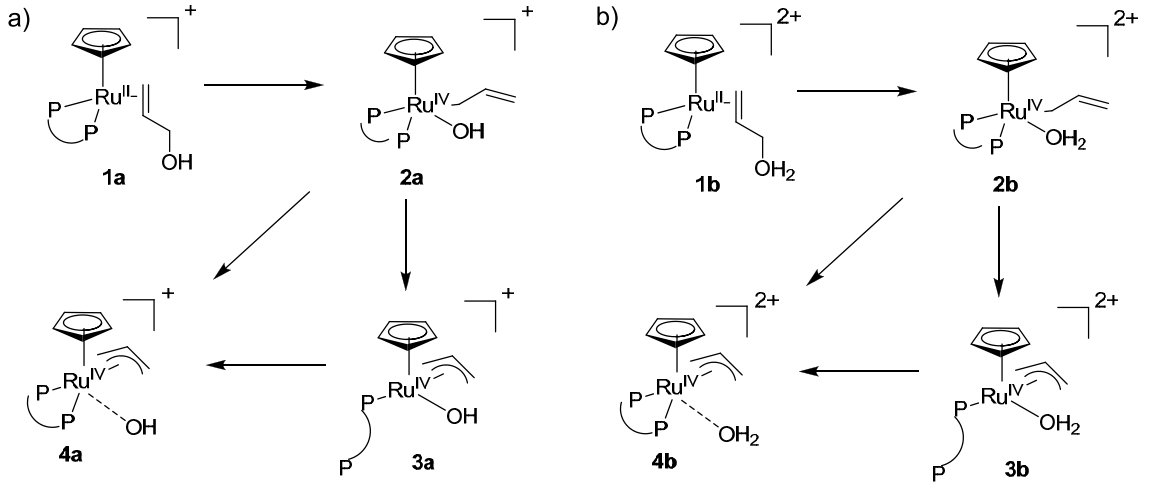


Scheme 7.2. Calculated reaction energies for O- and C-allylation of phenol with allyl alcohol.

It is indeed experimentally observed that at longer reaction times, O-allylated product is ultimately converted into the thermodynamic C-allylated end-product (Chapter 2). The rate of this conversion however, strongly depends on catalyst structure and experimental conditions. The calculated almost thermo-neutrality of O-allylation is in agreement with the observed partial conversion of substrates to O-allylated product and the reversibility of O-allylation. A higher than thermodynamic conversion to O-allylated product can only be achieved if the reaction product water is removed from the reaction medium, e.g. by phase separation (Chapters 2 and 3).

7.2.2 Oxidative addition of allyl alcohol

For the oxidative addition of allyl alcohol to Cp-ruthenium complexes with bidentate phosphine ligands (**1**) (Scheme 7.3), it is proposed that a σ-allyl species is initially formed (**2**), followed by a σ/π-allyl isomerization. Itoh and co-workers have reported a study on the oxidative addition of allyl halides to Cp-ruthenium complexes with two mono-phosphine ligands.[5] By means of NMR spectroscopy it was found that upon oxidative addition a σ-allyl species is initially formed which can proceed to a π-allyl species after dissociation of one of the phosphine ligands. For the Ru-based system described in this thesis, in order to prevent an undesired 20-electron species when the π-allyl species is formed, indeed one of the phosphines may dissociate, forming species **3**. Otherwise the hydroxide anion can be expelled from the coordination sphere to maintain an 18-electron species (**4**). Finally, ring slippage of the Cp anion from η^5- to η^3-coordination[9] would also give an 18-electron species with a



Scheme 7.3. Proposed intermediates in the oxidative addition of allyl alcohol for a) monocationic complexes in the absence of acid or b) dicationic complexes in the presence of acid. Solid bonds indicate coordination bonds, while dashed bonds represents bonds longer than coordination bonds.

π-allyl and a coordinating hydroxyl group. However, this species is very high in energy (energy difference relative to **1** ≥ 49 kcal/mol), as was determined by means of DFT-calculations, which seems to be an unlikely event and was not taken into further consideration.

Basset and co-workers have described the oxidative addition of allyl alcohol to a palladium(0) catalyst, both in neutral and acidic conditions. It was found that in the absence of strong acid, hydroxyl anions are produced, while in an acidic medium these hydroxyl anions rapidly react with the excess of protons to form water.

For the present ruthenium(II) catalyst system it is proposed that in a non-acidic system oxidative addition of allyl alcohol occurs without protonation of the Ru-bound allyl alcohol *a priori*. Addition of a strong acid, like *p*-toluenesulfonic acid (HOTs), accelerates the reaction in a major way. A strong acid will protonate the allyl alcohol during oxidative addition, thus facilitating this step by transforming the poor hydroxyl leaving group into the good leaving group water. Therefore, two different types of complexes have been calculated: one in the absence of acid (Scheme 7.3a) and one in the presence of acid (Scheme 7.3b). In order to save calculation time, the phenyl groups on phosphorous were replaced by hydrogens. This means that steric and electronic effects of substituents at P are not taken into account. The structure of the backbone of diphosphine ligands at Ru was experimentally shown to have a decisive influence on the activity and selectivity in phenol allylation. As in the actual ligands used the same or similar substituents at P are being used, it is believed that computation of energy profiles of catalytic pathways of model cationic catalyst complexes, $[(Cp)(H_2P(CH_2)_nPH_2)Ru(II)]^+$ will provide useful comparative insights into the effects of the diphosphine backbone structure on the catalytic performance of real catalyst complexes. Since DFT does not easily allow calculation of energy differences due to actual protonation events, the energy schemes shown were calculated for a completely monocationic complex catalytic pathway (Scheme 7.3a), simulating acid-free conditions or a completely dicationic complex pathway (Scheme 7.3b), simulating acidic conditions. In practice only a catalytic quantity of acid is applied and the acid will only play a co-catalytic role in converting certain intermediates.

7.2.3 Structural properties

The calculated molecular structures **2a**-**4a** and **2b**-**4b** are shown in Figure 7.1 for structures with a C_2-bridge in the phosphine bidentate ligand (1,2-diphosphinoethane = dpe). The

Table 7.1. Lengths of coordination bonds in calculated structures **2a**-**4b** for Ru(IV)Cp complexes with dpe as bidentate phosphine ligand.

	Bond lengths (Å)					
Structure	Ru1-O2	Ru1-P3	Ru1-P4	Ru1-C5	Ru1-C6	Ru1-C7
2a	2.156	2.316	2.314	2.240	3.075	4.020
3a	2.018	2.355	6.567	2.243	2.186	2.229
4a	2.954	2.612	2.296	2.388	2.202	2.233
2b	2.222	2.383	2.358	2.352	3.192	4.102
3b	2.264	2.462	6.540	2.271	2.219	2.292
4b	4.669	2.402	2.346	2.357	2.246	2.308

structures of the complexes with different chelating ligands dpm (= diphosphinomethane) and dpb (= 1,4-diphosphinobutane), show very similar geometrical characteristics and will not be discussed in detail. Selected calculated bond distances for the ruthenium complexes with the ligand dpe are listed in Table 7.1.

In the calculated Ru(IV) structures **2a**-**2b** σ-allyl coordination is present; only one carbon of the allyl group is within coordination distance from the Ru1 centre. In **3a**-**3b** one of the phosphine donor atoms is dissociated, and in **4a**-**4b** hydroxyl or water dissociation has occurred. For the structures **2** and **3**, the Ru1-O2 distance shows a typical coordination bond distance, but in structures **4a** and **4b**, the O2 atom is expelled from the Ru1 coordination sphere, to a distance of 2.9 and 4.7 Å, respectively. When the structures of **3a-3b** and **4a-4b** are compared with respect to the π-allyl group, it is observed that for the **3a-3b** structures an endo-allyl orientation is favored, while for **4a-4b** an exo-allyl orientation is found in the

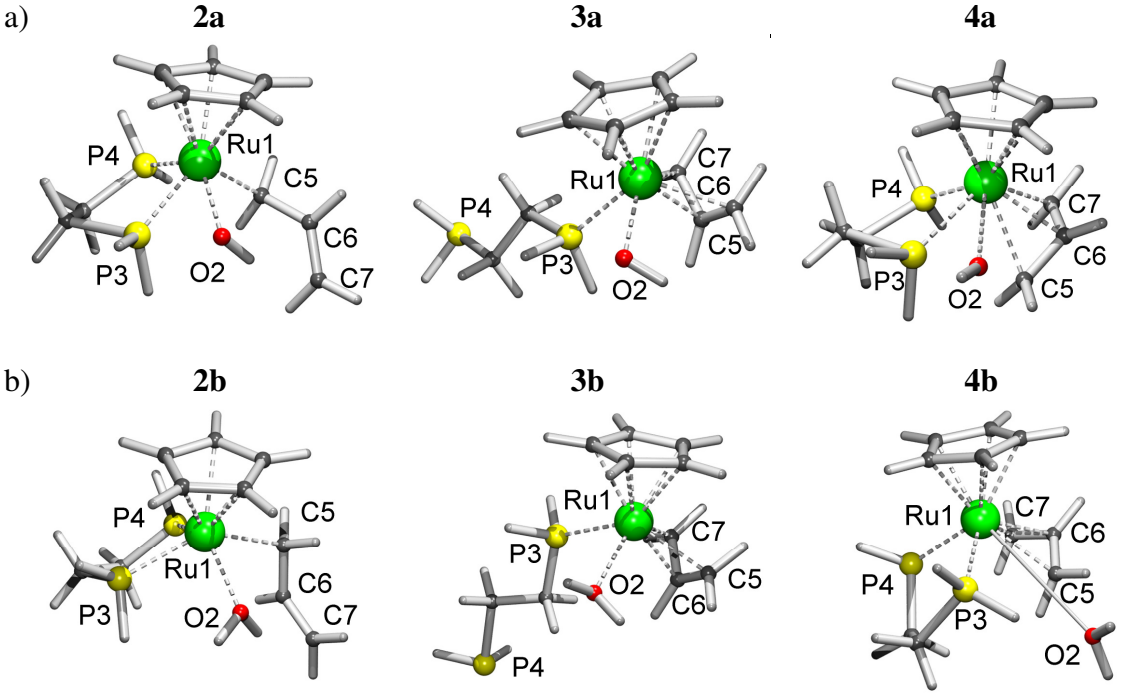


Figure 7.1. Calculated structure of **2**, **3** and **4** as a) monocationic species (absence of acid) and b) dicationic complexes (presence of acid).

minimized structure.

Another feature of the structure of **4a** is that the coordination of the two phosphine donors is not symmetric (Ru1-P3: 2.612 Å and Ru1-P4: 2.296 Å). The calculated local energy minimum apparently requires some mode of dissociation for one of the phosphine donors. This asymmetry is also influenced by the position of the hydroxyl anion. The O2-P3 distance is very short (1.762 Å) and apparently the anion interacts with the slightly electropositive phosphine donor. This interaction is observed for all the structures calculated, both with a hydroxyl anion as well as a phenolate anion. The calculation method does not allow complete dissociation of the anion from the cationic complex. Such features are not observed in the structure of **4b**, because the water molecule in this complex is clearly removed from the coordination sphere of the ruthenium centre (Ru1-O2 = 4.669 Å).

7.2.4 Energy diagrams for oxidative addition

The energy diagrams for oxidative addition of complexes with the ligands dpm, dpe, and dpb are shown in Scheme 7.4, both for the monocationic complex (Scheme 7.4a; absence of acid) as well as for the dicationic complex (Scheme 7.4b; presence of acid).

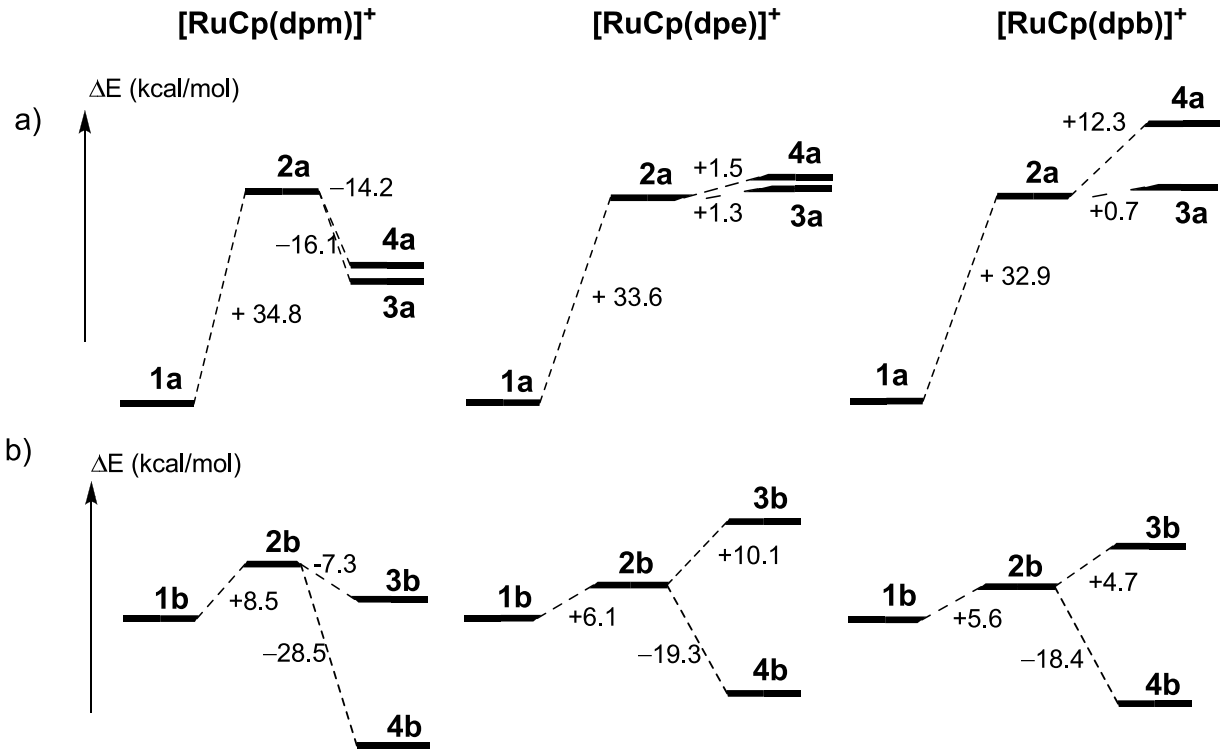
The cationic [RuCp(PP)(allyl alcohol)]$^+$ system

For the complex [RuCp(dpm)]$^+$ in the absence of acid, it is clear that phosphine dissociation gives the most stable Ru(IV) complex (**3a**). The strained 4-membered ring favors to open after oxidative addition to provide coordination space for π-allyl coordination. The preferred dissociation of one of the phosphine donors in a strained 4-membered chelate ring of a dpm ligand was observed in calculations on a Pd(dpm)-catalyzed Heck-type reaction.[10] A direct reaction from species **1a** to **3a** seems unlikely.[5]

The energy difference of +34.8 kcal/mol for oxidative addition seems to correspond with the observation that reaction temperatures of about 100 °C are needed for a reasonable reaction rate. The σ-allyl species with structure **2a** can thus probably be regarded as being close to the activated transition state barrier for the conversion of **1a** to **3a** or **4a**.

Phosphine dissociation is very likely to occur (from **2a** to **3a** = –16.1 kcal/mol) on forming a π-allyl species. Alternatively, and with a similar likelihood, dissociation of the basic hydroxide anion takes place to generate species **4a** (**2a** to **4a** = –14.2 kcal/mol).

The behavior of [RuCp(dpe)]$^+$ is somewhat different from that of [RuCp(dpm)]$^+$ in the absence of acid, showing no clear preference for any of the species (**2a**, **3a** or **4a**) formed after



Scheme 7.4. Energy diagrams for the oxidative addition step for [RuCp(PP)(allyl alcohol)]$^+$ complexes **1** in the a) absence of acid and b) presence of acid.

oxidative addition; both π-allyl species **3a** and **4a** are comparatively destabilized relative to σ-allyl species **2a**. This can be seen as a consequence of the larger P-Ru-P bite angle of the C_2 backbone bidentate phosphine ligand relative to dpm, which leads to less space available for coordination of the π-allyl moiety (occupying two binding sites) at Ru, and thus to destabilization of these species. The energy differences for these species are very small and interconversion between them are very well possible.

Finally, for the complex [RuCp(dpb)]$^+$ a similar energy difference between **1a** and **2a** (+ 32.9 kcal/mol) is observed as for both [RuCp(dpm)]$^+$ and [RuCp(dpe)]$^+$. Again, due to an even larger P-Ru-P bite angle of the C_4-diphosphine, the π-allyl species **3a** and, in particular **4a,** are raised in energy. The higher energy of species **4a** reflects that the coordination space at Ru is barely sufficient to accommodate the distant coordination of the anion with the coordination of both two bidentately coordinating entities, i.e. the C_4 backbone diphoshine and the π-allyl moiety. The coordination of both phosphine moieties is forced into an unsymmetrical coordination with different Ru-P distances, while the hydroxide anion is at close distance from one of the P donors.

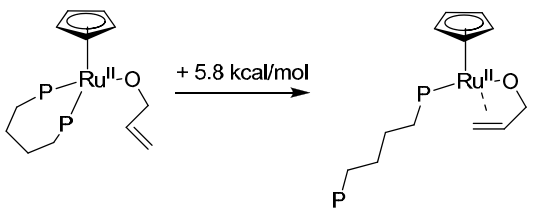
The dicationic [RuCp(PP)(allyl alcohol + H)]$^{2+}$ system

In the protonated dicationic species, simulating the presence of acid, the trends in the energy profiles of oxidative addition are significantly less dependent on the ligand (Scheme 7.3b, Figure 7.1b, Scheme 7.4b). This is in part a consequence of the DFT computational method in which only energy differences between fully protonated (or fully deprotonated) species can be calculated, while the protonation event itself cannot be considered.

The calculated energy difference between **1b** and **2b** is much smaller than between corresponding species **1a** and **2a** in the absence of added acid for all three of the complexes. The low energy barrier **1b** → **2b** demonstrates that formation of neutral H_2O drives the protonation in **2b** and it can thus be rationalized that the complexes strongly prefer to expel the water molecule from the coordination sphere forming dicationic species **4b** (–28.5 kcal/mol for [RuCp(dpm]$^{2+}$ and about –19 kcal/mol for [RuCp(dpe)]$^{2+}$ and [RuCp(dpb)]$^{2+}$) compared to phosphine dissociation species (**3b**). For the [RuCp(dpm)]$^{2+}$ complex, stronger stabilization of intermediate **4b** due to the small P-Ru-P angle (thus providing more space for (bidentate) π-allyl formation), is clearly reflected.

Allylation vs isomerization

The [RuCp(dppb)]$^{+}$ complex was experimentally demonstrated to be only active for allylation in the presence of strong acid (Chapter 2), where oxidative addition is highly promoted (**1b** to **2b** = +5.6 kcal/mol). In the absence of acid, [RuCp(dppb)]$^{+}$ is an active catalyst in the isomerization of allyl alcohols into carbonyl compounds, where phosphine dissociation from a Ru(II) is proposed to be an elementary step in the catalytic cycle.[11] Not only does the presence of acid promote the oxidative addition, but at the same time the allyl alcoholate formation (Scheme 7.5) will be inhibited in the presence of a strong acid. It is the combination of these two effects of acid that makes this catalyst system potentially attractive for the O-allylation of phenols. In non-acidic environment the bidentate coordination of allyl alcoholate, inducing phosphine dissociation has a relative low energy difference (+5.8 kcal/mol; Scheme 7.5) compared to the products of oxidative addition in the absence of strong acid **2a**-**4a**.

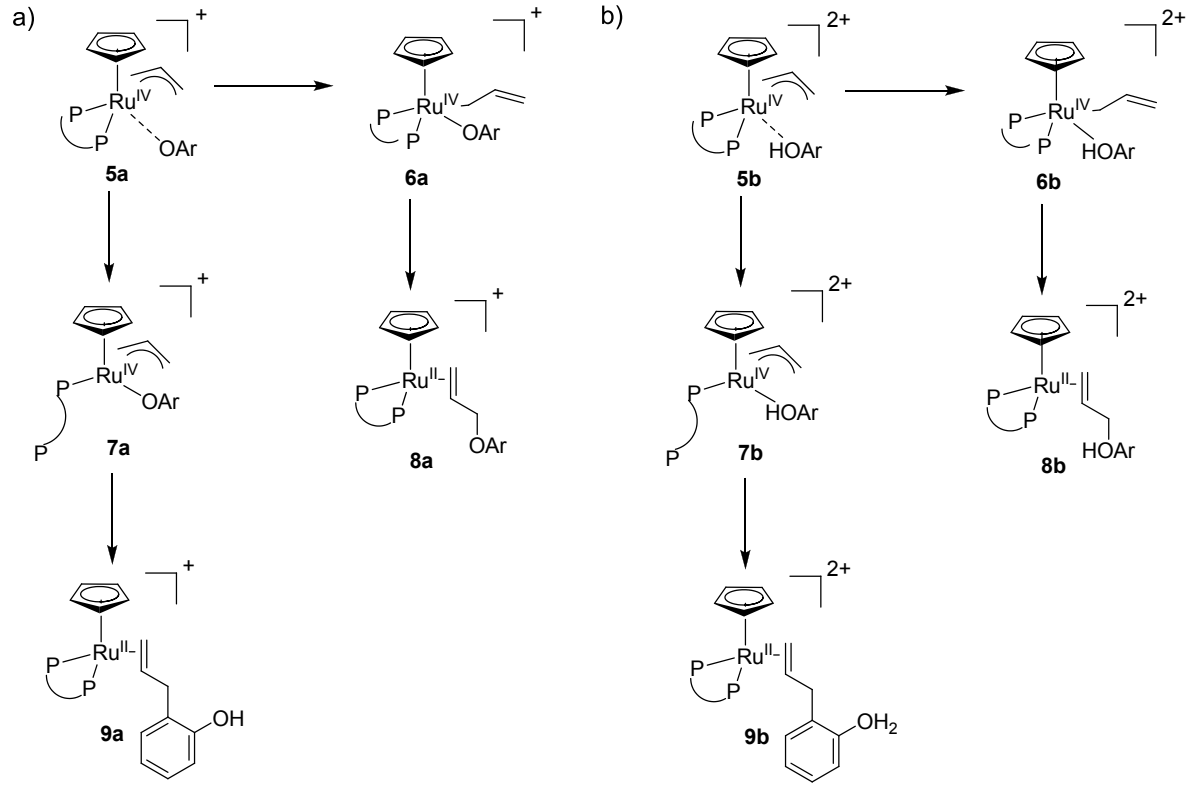


Scheme 7.5. Energy difference for phosphine dissociation during allyl alcohol isomerization into propanal.

However, when the reaction shown in Scheme 7.5 is calculated for complexes with the other ligands (dpm and dpe), also energy differences considerably lower than that of the oxidative addition step in the absence of acid are found (as low as −2.5 kcal/mol for dpm). Nevertheless, these complexes are experimentally found not to be active in the isomerization of allyl alcohol into propanal under the reaction conditions used for the allylation reactions (Chapter 2). The backbone flexibility of bidentate ligands with a relatively long (flexible) backbone is considered to be higher than that of ligands with a shorter backbone and thus phosphine dissociation will be relatively more likely. However, the backbone flexibility of the ligand will be reflected in an entropic factor of the free energy, which is not taken into consideration with the calculation method used. The degrees of freedom the reaction shown in Scheme 7.5, is probably greater for the complexes with a C_4-backbone ligand than that of complexes with shorter ligand backbones, thus favoring the isomerization reaction over the allylation reaction.

7.2.5 Reductive elimination towards O- and C-allylated products

After exchange of the hydroxyl for a phenolate anion, similar isomers will be formed as discussed for the hydroxyl-containing species (Scheme 7.6). Due to the high electrostatic interaction between the positively charged ruthenium(IV) center and the negatively charged



Scheme 7.6. Reductive elimination towards either O-allylated or C-allylated products.a) in absence of acid, b) in the presence of acid.

phenolate ion, especially in apolar solvents like toluene, coordination of the phenolate will compete with coordination of the phosphine and allyl ligand. Again, in order to prevent a highly unfavored 20-electron species, either the σ-allyl species **6a**-**6b** will be formed or phosphine dissociation will occur (**7a**-**7b**), depending on the stability of the chelate ring. From the σ-allyl species, reductive elimination can occur, which is the microscopic reverse of the oxidative addition of allyl ethers, forming ruthenium-bound allyl phenyl ether **8a**-**8b**. This reaction is highly exothermic, as expected for a microscopic reverse of a highly endothermic oxidative addition.

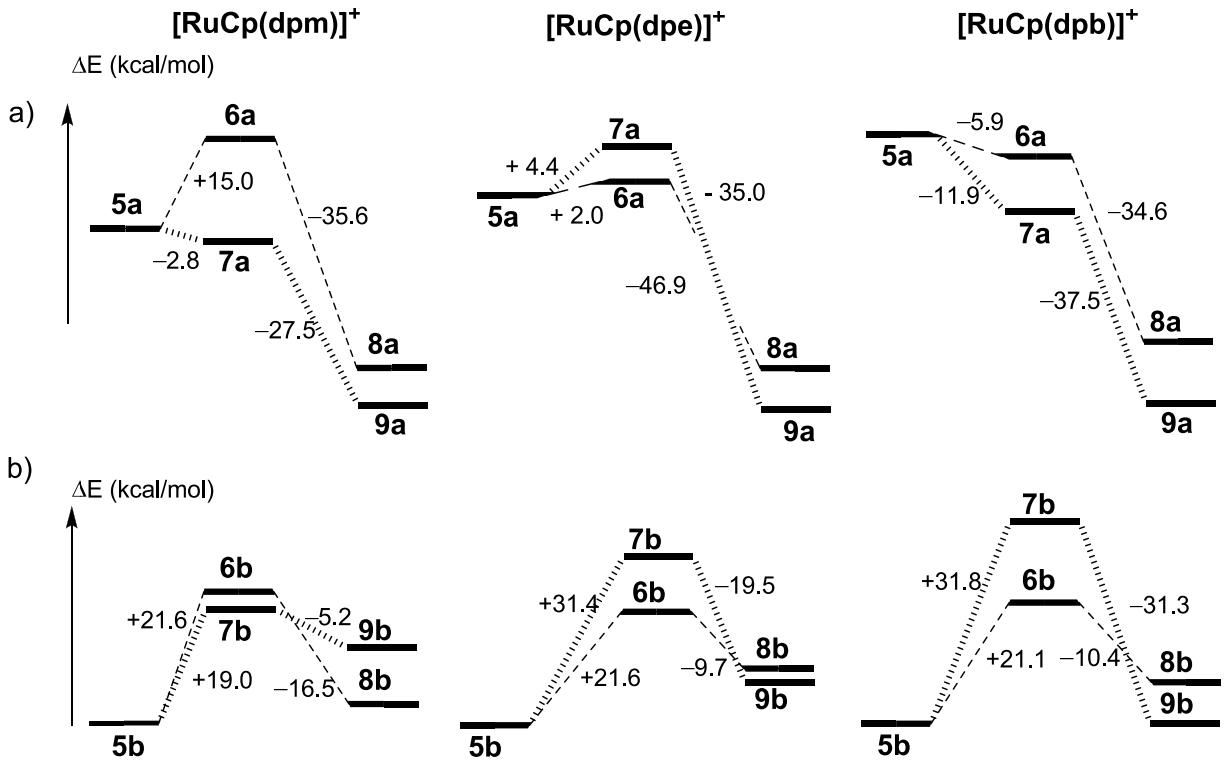
When instead of forming a σ-allyl species phosphine dissociation occurs (**7a**-**7b**), C-allylated products may be formed (**9a**-**9b**), as was discussed in Chapter 2 and 3. The molecular structures of the complexes resemble those obtained for the intermediates in oxidative addition (Figure 7.1) and are not discussed in detail. Similar to the oxidative addition step, both the monocationic complexes (Scheme 7.7a; absence of acid) as well as the dicationic complexes (Scheme 7.7b; presence of acid) were calculated.

7.2.6 Energy diagrams for reductive elimination

The cationic [RuCp(PP)(allyl)(OPh)]$^+$ system

For the [RuCp(dpm)(allyl)(OPh)]$^+$ complex, in the absence of an acidic proton, the Ru(IV) intermediate in which one phosphine donor is dissociated (**7a**; Scheme 7.7a) lies considerably lower in energy than the Ru(IV)(σ-allyl) intermediate (**6a**), caused by the release of ring strain of the coordinated ligand as observed for the oxidative addition step (Scheme 7.4). Reductive elimination leads to either species **8a** or **9a**, of which the latter is thermodynamically favored. Since formation of **7a** is clearly favored, formation of **9a** is also more likely, which corresponds with the observation that [RuCp(dppm)]$^+$ selectively forms C-allylated product.

[RuCp(dpe)]$^+$ shows again an energy profile that is very different from that of [RuCp(dpm]$^+$. Intermediates **5a**, **6a** and **7a** have a relatively small energy difference and **7a** lies slightly higher in energy. This lack of preference corresponds with the experimental results reported in Chapter 2. The use of [RuCp(dppe)]$^+$ as a catalyst in the allylation of phenol shows no initial preference for either O- or C-allylation. The reductive elimination step is highly exothermic towards species **8a** and **9a** of which **9a** again is the lowest in energy (−35.0 and −46.9 kcal/mol respectively).



Scheme 7.7. Energy diagrams for the reductive elimination step towards [RuCp(PP)(allyl ether)]$^{n+}$ (**8**) and [RuCp(PP)(*o*-allylphenol)]$^{n+}$ (**9**) complexes in a) the absence of acid and b) the presence of acid.

Finally, the [RuCp(dpb)]$^+$ cationic species shows a lowering in energy going from **5a** to either **6a** or **7a**, of which the latter is lowest in energy in the absence of acid. Reductive elimination to form **8a** or **9a** is again highly exothermic (−34.6 and −37.5 kcal/mol respectively).

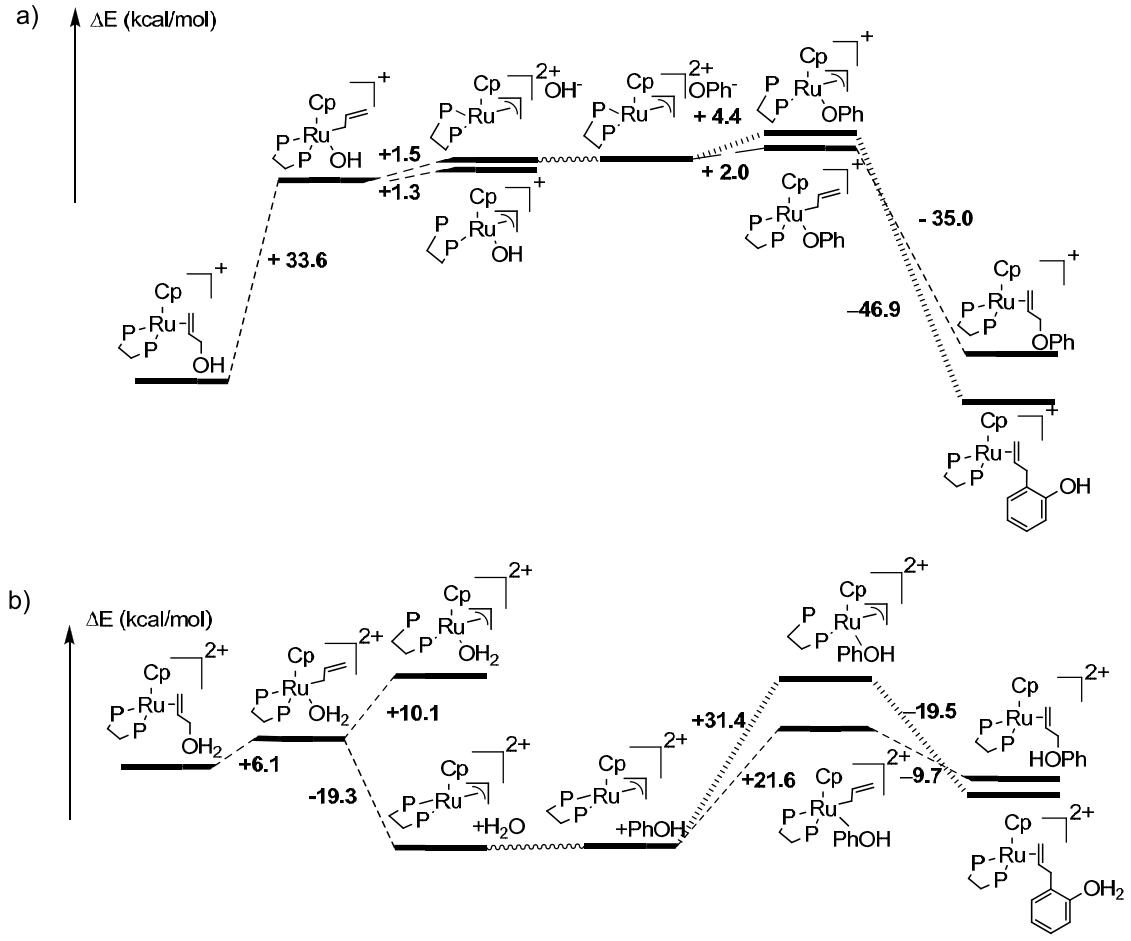
The dicationic [RuCp(PP)(allyl)(HOPh)]$^{2+}$ system

In the presence of acid (Scheme 7.7b), isomerization of the very stable resting state **5b** to either **6b** or **7b** is a highly endothermic process for the three complexes (around + 20 to + 32 kcal/mol). This phenomenon indicates that from **5b** it is not likely that a phenol will coordinate onto the Ru(IV) center. The approach of a phenol molecule towards the Ru(IV) center must be accompanied by a simultaneous deprotonation and subsequent formation and coordination of a phenolate anion. It is interesting to see that the energy difference between **6b** and **7b** increases with increasingly larger bite angles. When the phenol approaches the Ru(IV) center, the increase in congestion of the ligands at Ru(IV) apparently favors π- to σ-allyl isomerization over phosphine dissociation. As it is proposed that O-allylation proceeds via a Ru(IV) σ-allyl species, this energy trend corresponds with the experimental observation that in the presence of acid complexes with large bite angles favor O-allylation over C-allylation. Reductive elimination from **6b** or **7b** leads to product-bound species **8b** and **9b** and is exothermic in all cases shown in Scheme 7.7 (−5 to −31 kcal/mol).

In the absence of acid product **8a** is always about 10 kcal/mol higher in energy than **9a**, as it should be according to the results shown in Scheme 7.2. In **8b** and **9b**, however, repulsion between the proton located at the O-atom of the substrate and the positively charged Ru(II) ion leads to the different energies of both **8b** and **9b** compared to the acid-free situation. In practice, with a catalytic quantity of protons, deprotonation will of course readily occur during the product forming step, preparing the proton for its action in the next catalytic cycle.

7.2.7 Total energy profile from substrates to products and discussion

In Scheme 7.8, the oxidative addition and reductive elimination step for the $[RuCp(dpe)]^+$ complex are combined to illustrate the total energy profile of a catalytic phenol allylation pathway with allyl alcohol as the allylation agent. The pathway to O- and C-allylated product is given for both the monocationic (situtation a) as well as for the dicationic (situation b) catalyst system.



Scheme 7.8. Total energy profile of O- and C-allylation of phenol with allyl alcohol with $[RuCp(dpe)]^+$ as the catalyst a) in the absence and b) in the presence of acid.

For the cationic $[CpRu(dpe)(allyl\ alcohol)]^+$ system, the energy diagram is shown in Scheme 7.8a, simulating the catalyst system in the absence of acid. The endothermic oxidative addition towards Ru(IV), followed by the exothermic reductive elimination back to Ru(II) species is clearly observed. Although the energy difference due to exchange of the hydroxide anion with a phenolate anion is not taken into account, it is expected that this difference will be relatively small. The overall energy difference between initial and final state of the elementary reactions (+2.0 kcal/mol for O-allylation; −7.4 kcal/mol for C-allylation) must correspond with that of the overall reaction, shown in Scheme 7.2 (+ 0.1 kcal/mol for O-allylation; −8.8 kcal/mol for C-allylation).

For the dicationic $[RuCp(dpe)(allyl\ alcohol + H)]^{2+}$ system, simulating the presence of acid (Scheme 7.8b), such a correspondence with the overall allylation process, is less clear (−1.3 kcal/mol for both O- and C-allylation). Apparently, protonation of the coordinated allyl alcohol, but also the allyl phenyl ether and *ortho*-allylphenol changes the calculated energy differences between such species significantly. As indicated above, this can be seen as a limitation of the calculations as only fully protonated species have been calculated in Scheme 7.8b, while the protonation event itself cannot be calculated.

Nevertheless, even within the limitations set by DFT energy considerations several features of the phenol allylation reaction are satisfyingly illustrated. The promoting effect of protons on the oxidative addition by lowering its energy barrier is clearly observed, while the high stability of the $[Ru(IV)Cp(PP)(\pi\text{-allyl})]^{2+}$ species is also clearly recognized in the energy calculations. Furthermore, the competition between the various elementary organometallic process steps such as anion dissociation, dissociation of a phosphine moiety and σ-allyl$\rightarrow$ π-allyl rearrangement at the Ru centre are clearly rationalized as important activity- and selectivity-determining catalytic indicators.

The activation of allyl phenyl ether under product-forming conditions gives intermediates that again are involved in the same competitive elementary processes of anion- or phosphine dissociation and π-allyl $\rightarrow$ σ-allyl isomerization, ultimately leading to the thermodynamic C-allylated final product, unless the catalyst characteristics are such that the pathway towards C-allylated product is fully blocked. The present computational results are a rationalization of the notion that the pathway to C-allylated products requires ample coordination space at Ru(IV) made possible either by using small bite angle diphosphine ligands or ligands that form relatively labile chelates. It is suggested that ample accessible coordination space allows an initially O-coordinated phenoxy ligand to become strongly electrophilically activated by

Ru(IV) and thus to become attacked by the (bidentate) π-allyl moiety in the same coordination sphere forming C-allylated product (Chapters 2, 3). The alternative pathway of phenolate coordination to enforce π-allyl rearrangement into σ-allyl, and subsequent reductive elimination to allyl phenyl ether, cannot compete when ample space is available.

Apart from chelate stability of the bidentate ligands also their bulkiness will probably be important ligand parameters to limit accessible coordination space at the $[Ru(IV)Cp(PP)(allyl)]^{2+}$ center, such that phenoxyl coordination readily enforces a π-allyl to σ-allyl rearrangement. Steric and electronic properties of the ligand will be interrelated and their effects on catalytic performance may be difficult to predict; the DFT calculations presented in this chapter until now only involve $H_2P(CH_2)_nPH_2$ ligands, but it is clear that more advanced DFT calculations should be undertaken to investigate the predicted catalytic consequences of using "real life" ligands. Unfortunately, such extended ligand systems and their complexes were not within our computational possibilities.

One minor modification, relatively easy to handle computationally, involved the addition of methyl-substituents in the ligand backbone. In the next section the computational study of the effect of geminal substitution on the reductive elimination step is discussed.

7.2.8 Complexes having ligands with gem dialkyl substituted backbones

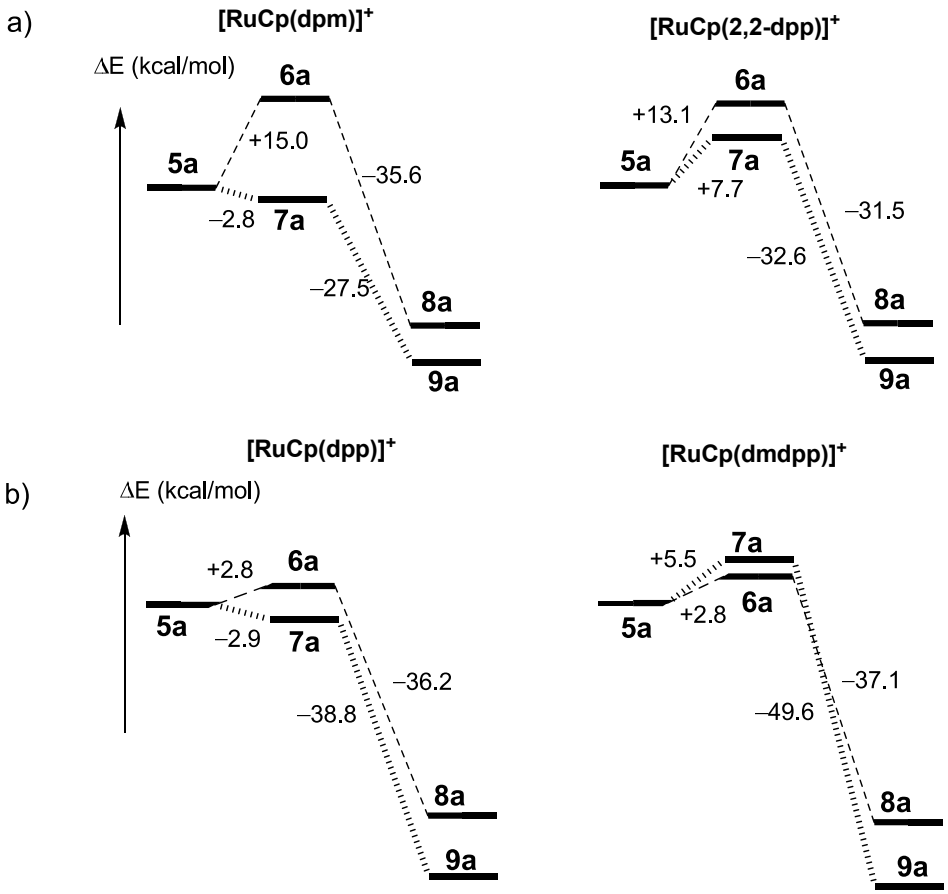
In Chapter 3 it is reported that the incorporation of dialkyl geminal substituents in the diphosphine ligand backbone has a dramatic effect on especially the selectivity of the phenol allylation reaction.

It was proposed that geminal backbone substituents increase the chelate coordination stability and it was concluded that $[RuCp(PP)]^+$ complexes with stable chelating diphosphine ligands are more selective towards O-allylation. Especially the geminal dialkyl substitution of the ligand C_1- and C_3-backbones resulted in a dramatic increase in the selectivity of the catalysts for O-allylation. It would be interesting to corroborate this selectivity-improving effect of dialkyl substituents in the ligand's backbone by means of DFT-calculations.

The computational results discussed in the previous sections imply that the selectivity for allylation of phenols is primarily determined by the allyl phenyl ether reductive elimination, i.e. the product-forming step. Therefore, the focus of the calculations is on this step with hope to shed some light on the origin of this intriguing and subtle ligand effect on the selectivity in the allylation of phenols.

The energy profile of the reductive elimination of *o*-allyl phenol (**9a**) or allyl phenyl ether (**8a**) from a $[Ru(IV)Cp(PP)(allyl)(OPh)]^+$ species towards Ru(II)-bound product species, has been calculated for a Ru complex with a C_1- and C_3-geminal dimethyl-substituted bidentate phosphine ligand and is compared with the energy profile obtained with the respective unsubstituted ligands (Scheme 7.9).

For the unsubstituted dpm ligand it was calculated that species **7a** is lower in energy relative to **6a** (**6a** to **7a** = –17.8 kcal/mol). For the complex with the substituted 2,2-dpp ligand, phosphine dissociation upon phenolate coordination apparently is considerably less favored, since the energy difference between **6a** and **7a** is only –5.4 kcal/mol. The increased phosphine coordination strength towards Ru(IV) by *gem* dimethyl substitution at de C_1-backbone of dpm can be rationalized by the higher basicity at the phosphines due to the two electron-donating methyl substituents. The increase in chelate stability should indeed result in a catalyst which has a higher selectivity for O-allylation. However, as can be seen in Scheme 7.9a, phosphine



Scheme 7.9. Energy diagrams for the reductive elimination step for $[RuCp(PP)(allyl\ alcohol)]^+$ complexes in the absence of acid**.** Comparison between (a) $[RuCp(dpm)]^+$ (already shown in Scheme 7.3) and $[RuCp(2,2\text{-}dpp)]^+$, and (b) between $[RuCp(dpp)]^+$ and $[RuCp(dmdpp)]^+$.

dissociation upon phenolate coordination ultimately giving *o*-allylphenol (**9a**), still is about 5.4 kcal/mol advantaged over π-allyl → σ-allyl isomerization (**6a**). It thus appears that a consideration of the energy profiles alone, although directionally right, is quantitatively insufficient to explain the strong deviations in selectivity due to the *gem* substituents in the backbone of this catalyst's ligand.

It can be seen from Scheme 7.9b that diphosphine coordination of the $[RuCp(dmdpp)]^+$-complex is again somewhat stronger, i.e. dissociation of a phosphine moiety upon coordination of phenolate has a higher energy, compared to that of the $[RuCp(dpp)]^+$-complex. This could be due to an electronic effect at the phosphine donor or a slight structural difference of the energy-minimized configuration. Although in the catalytic pathway with the geminal substituted ligand phosphine dissociation upon phenolate coordination (pathway **5a** → **7a** → **9a**) has only a slightly higher (< 3 kcal/mol) calculated energy barrier than the π-allyl → σ-allyl isomerization (pathway **5a** → **6a** → **8a**), it is believed that the difference in energy profile is rather insignificant, although again directionally right, to explain the experimentally observed strong increase in O-allylation selectivity.

In addition to the DFT energy argument to compare the two reaction pathways, it is necessary to consider an entropic difference in the dissociation of one phosphine donor from Ru between the *gem* dimethyl-substituted and unsubstituted ligand complexes. Due to the restricted configurational freedom of the partial dissociated phosphine entity of the *gem*-dialkyl substituted ligand in **7a**, the entropy gain in dissociation of one phosphine donor must be significantly smaller than for the complex of the unsubstituted (flexible) ligand. Thus pathway **5a** → **7a** → **9a** becomes more unlikely to follow due to this unfavorable entropic factor in the *gem* disubstituted ligand. The importance of the entropy factor was already mentioned for the allylation vs isomerization effect with the $[RuCp(dpb)]^+$ complex. However, entropic effects are not taken into account with the standard DFT methodology applied here and more advanced DFT computational methods should be used to study the role of entropy also in the other elementary steps of the catalytic cycle.

7.3 Conclusions

With the theoretical data presented and supported with a vast quantity of experimental results described in the previous chapters, a detailed mechanistic picture is drawn that explains the observed features of the allylation of phenol with allyl alcohol using $[RuCp(PP)]^+$ complexes. Phosphine dissociation plays a crucial role in determining the activity and especially

selectivity of the catalysts and has a dramatic effect on the (de)stabilization of the energy levels of the intermediates in the catalytic cycle. The effects of changing the chelating phosphine ligand are observed for both the oxidative addition step as well as the reductive elimination, especially for the system calculated in the absence of acid. The system calculated in the presence of acid shows promotion of the oxidative addition step. The incorporation of *gem*-dialkyl substituted phosphine ligands in the catalysts stabilizes phosphine coordination in the Ru(IV) state, since phosphine dissociation becomes less favored. However, entropic effects will change the energy levels considerably, but these effects cannot be illustrated with the calculation method used here. Attempts should be undertaken to calculate these entropic effects with more detailed and extensive calculation methods.

7.4 Experimental

Theoretical methods. The potential energy surfaces (PESs) corresponding to the processes involved in the allylation of phenols with allyl alcohol have been explored using density functional theory (DFT)[12,13] with the Becke and Perdew (BP) functional.[14,15] All the geometry optimizations were carried out using Pople's 6-31G* (d,p) for H, C, O and P atoms[16] and the LANL2DZ effective core potential for ruthenium.[17-19] All of the geometrical parameters were fully optimized, and all of the structures located on the PESs were characterized as minima. No constraints to bonds, angles or dihedral angles were applied in the calculations, and all atoms were free to optimize. The SPARTAN '04 package (Wavefunction, Inc; www.wavefun.com) was used to carry out the calculations.

7.5 References

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8

Palladium-diphosphine complexes as catalysts for allylations with allyl alcohol

Abstract
Several palladium complexes with bidentate phosphine ligands were tested for their activity in the O-allylation of phenols with allyl alcohol. The use of C_3-bridged bidentate phosphine ligands results in very high selectivity for O-allylation. The reactions do not require stoichiometric amounts of additives to control the chemoselectivity. Especially, catalysts with *gem*-dialkyl substituted C_3-bridged bidentate phosphine ligands perform very well, resulting in a (equilibrium) conversion of ~50% of phenol with a selectivity of 99% for O-allylation. The use of diallyl ether as the allylating agent results in a significant increase in phenol conversion while maintaining high selectivity for O-allylation. Apart from $Pd(OAc)_2$ as catalyst precursor, $Pd(dba)_2$ was also employed, making it possible to use other types of phosphine or phosphite ligands. With the palladium catalytic system not only phenol, but also aliphatic alcohols can be efficiently allylated, as well as aromatic and aliphatic amines.

8.1 Introduction

Allylation reactions of phenols are mostly reported with allylating agents such as allyl chloride or allyl acetate and stoichiometric amounts of base are added to induce selectivity for O-allylation.[1,2] Numerous allylation reactions, generally known as the Tsuji-Trost reaction, have been reported using palladium catalysts.[3-5] From an atom-efficient point of view, it would be desirable to use allyl alcohol as the allylating agent. Several palladium systems have been reported to be able to use allyl alcohol as an allylating agent.[6-10] In the cases where phenols are used as the substrate, stoichiometric amounts of base are necessary to induce chemoselectivity towards O-allylation, inevitably resulting in inorganic waste.[8] In the absence of base, C-allylation occurs,[9] a feature also observed with ruthenium-based systems.[11] For the ruthenium-based system reported in the previous chapters, a large variety of ligands were tested; the role of the ligand appeared to be of great importance for the activity and selectivity and it was shown that with only minor changes in the ligand structure, dramatic effects on both activity and selectivity were accomplished. Restricted coordination space at the ruthenium center favors the formation of the O-allylated product, which could be achieved by using ligands that either have a large bite angle or form strong chelates. For palladium however, the use of $Pd(OAc)_2$ for the allylation of phenol-type substrates has only been reported with monodentate phosphine ligands.[7-9]

In this chapter, the catalytic results are discussed of a palladium system with a selection from the ligand library used for the ruthenium complexes; the activity and selectivity for O-allylation as a function of the ligand is reported.

8.2 Results and discussion

8.2.1 Catalysis with $Pd(OAc)_2$ as catalyst precursor

The palladium precatalysts were formed *in situ* by addition of a bidentate phosphine ligand to $Pd(OAc)_2$. This results in the initial formation of the species $[Pd(II)(OAc)_2(PP)]$, but it has been reported that these complexes can be reduced in the presence of an excess of phosphine ligands to form Pd(0) complexes, acetic anhydride and phosphine oxides.[12,13] This process is slower for bidentate ligands than for monodentate ligands and does not occur without an excess of phosphine ligand. Immediate stabilization of the formed Pd(0) species with ligand

or substrate, or subsequent uptake into the catalytic cycle is highly beneficial for the reduction reaction to occur.[13]

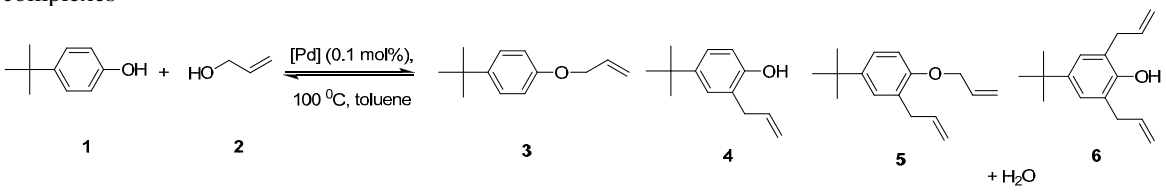
A palladium over diphosphine ligand ratio of 1/4 was found to give optimal activity for the allylation reaction shown in Table 8.1. The use of $Pd(OAc)_2$ to bidentate phosphine ratios of 1/2 or even 1/1 results in a lower stability of the catalyst; the conversions are significantly lower and precipitation of metallic palladium (plating) is more pronounced. The results of the use of different phosphine ligands with $Pd(OAc)_2$ in the catalytic allylation of 4-*tert*-butylphenol (**1**) are summarized in Table 8.1.

The addition of dppm as a bidentate phosphine ligand to $Pd(OAc)_2$ (entry 1) results in the formation of a selective catalyst for O-allylation of phenol with allyl alcohol, but, the conversion of **1** is relatively low. The solution turned intensely red, indicating the formation of Pd(I) dimers.[14,15] When dppe is used as the ligand (entry 2), the resulting catalytic activity is very low. Formation of $[Pd(dppe)(OAc)_2]$ is slow, due to the relatively high stability of a $[Pd(dppe)_2](OAc)_2$ intermediate.[16] This phenomenon may prevent proper formation of active catalyst. When $[Pd(dppe)(OAc)_2]$ is preformed and used as a catalyst in the presence of three equivalents of dppe, activity for allylation remains very low.

Indeed, when the bridge length of the bidentate ligand is increased to a C_3-fragment in dppp (entry 3) the conversion increases, with maintenance of the very high selectivity. Only O-allylation is observed, making this the first Pd-based catalyst that is selective for O-allylation without the need for any stoichiometric additives.

When using the C_4-bridged ligand dppb (entry 4), the conversion of **1** is even higher, but the

Table 8.1. Reaction of 4-*tert*-butylphenol (**1**) with allyl alcohol (**2**) catalyzed by different Pd –diphosphine complexes [a]



entry	$Pd(OAc)_2$ + PP PP =	conversion of **1** (%)			selectivity (%) **3**	**4-6**	**3**	**4-6**	**3**	**4-6**
		1 h	3 h	6 h	1 h		3 h		6 h	
1	dppm	2	6	13	100	0	100	0	100	0
2	dppe	0	0	2	-	-	-	-	100	0
3	dppp	15	20	26	100	0	100	0	100	0
4	dppb	21	35	53	100	0	87	13	72	28
5	2 PPh_3	28	44	56	65	35	29	71	16	84

[a] Reaction conditions: ratio 4-*tert*-butylphenol/allyl alcohol/$Pd(OAc)_2$/PP = 1000/2000/1/4, toluene, 100 °C.

selectivity for O-allylation is decreased. Finally, the catalyst with the monodentate ligand triphenylphosphine (entry 5) has a low selectivity for the desired O-allyl ether; after six hours mainly C-allylated products are obtained, in agreement with earlier studies with similar substrates.[9]

A dramatic effect on both activity and selectivity is thus observed by simply changing the bridge length of the bidentate ligand. A drying agent is not required and high catalytic activity is observed even with a low catalyst concentration of 0.1 mol% of Pd on **1**. However, the stability of these palladium catalysts is different from the Ru-complexes (Chapter 2-5). For the ruthenium-based catalysts high turnover numbers could be achieved when using high substrate over catalyst ratios. For the Pd-based catalysts described here increasing the substrate over catalyst ratio does not lead to significantly higher turnover numbers and a maximum TON of ~800 is reached. During all reactions some plating of palladium metal was visible, which most likely is the major deactivation pathway of the catalyst.

Although the selectivity of the palladium system is already high when dppp is used as the ligand, the use of kinetically more stable chelating ligands might aid in further stabilization of the intermediate zerovalent palladium complexes and in preventing plating to palladium black. The results of the catalytic reactions using the *gem*-dialkyl ligands are shown in Table 8.2.

The conversion of **1** by the catalytic system with dppp increases when longer reaction times (22 h) are used (entry 1). For the catalyst with dppdmp (entry 2) as the bidentate phosphine ligand, initial conversion after one hour is very similar to that of the reaction with dppp as the ligand. This indicates a similar rate constant and thus a comparable activity of these catalysts. Higher conversions after 6 and 22 hours are observed for the catalyst with dppdmp, indicating

Table 8.2. Reaction of 4-*tert*-butylphenol (**1**) with allyl alcohol (**2**) catalyzed by different Pd–diphosphine complexes starting from $Pd(OAc)_2$ [a]

entry	$Pd(OAc)_2$ + PP PP =	solvent	conversion of **1** (%)			selectivity (%)[b]			
						3	**4-6**	**3**	**4-6**
			1 h	6 h	22 h	6 h		22 h	
1	dppp	toluene	15	26	38	100	0	94	6
2	dppdmp	toluene	16	41	58	99	1	95	5
3	dppdep	toluene	14	38	50	99	1	99	1
4[c]	dppdmp	toluene	0	0	0	-	-	-	-
5	dppdmp	n-heptane	11	31	54	100	0	99	1
6	dppdep	n-heptane	9	23	56	99	1	97	3
7[c]	dppdep	n-heptane	4	43	80	99	1	85	15

[a] Reaction conditions: ratio 4-*tert*-butylphenol/allyl alcohol/$Pd(OAc)_2$/PP = 1000/2000/1/4, toluene, 100 °C
[b] selectivity after 1 hour 100% for **3**
[c] *p*-toluenesulfonic acid was added (10 eq on Pd)
[d] diallyl ether was used as the allyl donor (ration 4-*tert*-butylphenol / diallyl ether = 1/1).

the formation of a more stable catalyst compared to $Pd(OAc)_2$ with dppp. The use of the *gem*-diethyl substituted phosphine ligand dppdep (entry 3), also leads to higher conversion of **1**. When a yield of about 50% of **3** is obtained, equilibrium is reached and further conversion of **1** into **3** is halted. In contrast to the cationic ruthenium-based system, the addition of a strong acid to the reaction mixture does not increase the rate of the reaction, but actually inhibits the catalyst for allylation (entry 4). When the acid is added after one hour reaction time, the reactivity of the catalyst is completely halted from that moment on, including conversion of O-allylated products into the thermodynamically favored C-allylated products.

The equilibrium reaction of O-allylation is governed by the amount of water that is soluble in the reaction mixture. The use of the apolar solvent toluene limits the solubility of this water in the reaction mixture and the water forms a separate phase. The more apolar solvent *n*-heptane can also be used as a solvent (entry 5-6); this results in a lower conversion after 1 and 6 hours, but after 22 hours conversions are very similar to those obtained for the reactions in toluene. Apparently, activation of the catalyst proceeds less efficient in *n*-heptane as compared to toluene The use of dppdmp or dppdep in this reaction medium results a very similar selectivity for O-allylation after 22 hours. Although a water scavenger is not needed in this system, water removal from the system would probably be beneficial to obtain higher yields of **3** in a batch process and higher conversion per pass in a continuous process. When diallyl ether is used as the allylating agent (entry 7), the conversion of **1** and the yield of **3** after 22 h is indeed increased significantly in agreement with the lower quantity of water produced relative to that using allyl alcohol as allylation agent. However, at high phenol conversion and very long reaction time, C-allylated product **4** is also formed.

8.2.2 Catalysis with $Pd(dba)_2$ as catalyst precursor

The use of phosphine ligands that are not oxidized easily, such as *o*-anisylphosphines previously used for Pd-catalyzed olefin-carbon monoxide copolymerization,[17] or the use of triphenylphosphite in combination with $Pd(OAc)_2$ does not yield active catalysts for allylation. In combination with the Pd(0) precursor $Pd(dba)_2$, (dba = dibenzylideneacetone) however, the use of these ligands does result in an active catalytic system and the results are shown in Table 8.3.

When dppdmp is added to $Pd(dba)_2$ (entry 1), a similar conversion with high selectivity is reached compared to the reactions in which $Pd(OAc)_2$ is used as precursor, indicating that *in situ* the same catalyst is obtained. For *o*-MeOdppp (entry 2) and *o*-MeOdppdmp (entry 3), the

Table 8.3. Reaction of 4-*tert*-butylphenol (**1**) with allyl alcohol (**2**) catalyzed by different Pd –diphosphine complexes starting from $Pd(dba)_2$ [a]

entry	$Pd(dba)_2$ + PP PP =	conversion of **1** after 22 h (%)	selectivity after 22 hours (%)	
			3	**4-6**
1	dppdmp	49	96	4
2	*o*-MeOdppp	10	100	0
3	*o*-MeOdppdmp	12	100	0
4	2 P(*o*-An)$_3$	17	100	0
5	*p*-MeOdppp	38	100	0
6	*o*-Medppp	72	71	29
7	2 P(OPh)$_3$	11	100	0

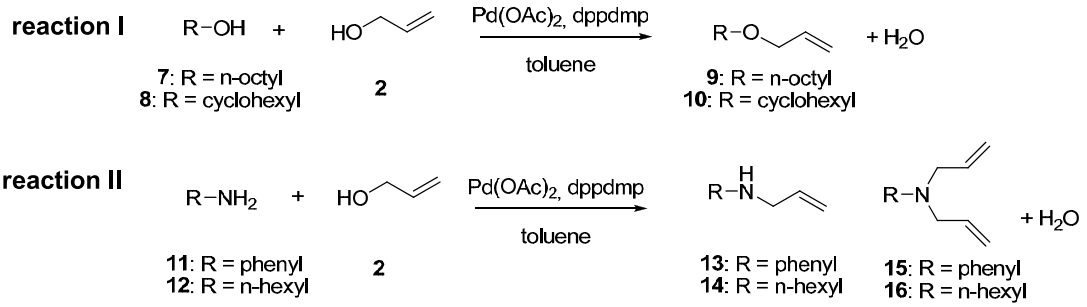
[a] Reaction conditions: ratio 4-*tert*-butylphenol/allyl alcohol/$Pd(dba)_2$/PP = 1000/2000/1/4, toluene, 100 °C

anisyl analogues of dppp and dppdmp, only a very low conversion is observed, albeit with high selectivity for **3**. The addition of monodentate tris(*o*-anisyl)phosphine as the ligand (entry 4) results in a slightly higher conversion of **1**, but when compared to its unsubstituted analogue triphenylphosphine in combination with Pd(II) (Table 8.1; entry 5), the resulting catalyst reaches considerably lower conversion. In order to investigate steric versus electronic effects of the different ligands on the catalytic results, *p*-MeOdppp was used as ligand (entry 5). In this case the conversion of **1** is considerably higher than for *o*-MeOdppp and comparable to that observed for the combination of $Pd(OAc)_2$ with dppp as the ligand (Table 1; entry 3); therefore an electronic effect can be excluded. The addition of *o*-Medppp (entry 6) results in a considerably higher conversion than when *o*-MeOdppp is used. The increase of steric bulk around the palladium centre therefore seems not to be the sole reason for the low activity of the catalyst with *o*-anisyl ligands, since an *o*-tolyl group is considered to cause similar steric hindrance around the metal centre compared to an o-anisyl group. If such steric hinderance would pose a limiting factor on activation, the catalyst with o-Medppp would be less active compared to the catalyst with dppp, which is not the case. Most likely coordination of the methoxy group, as already reported for similar complexes,[18] hampers activation of allyl alcohol at the palladium centre and thus results in lower catalytic activity. The use of electron-withdrawing triphenylphosphite as the ligand (entry 7) for catalytic allylation also results in very low conversion of **1**. From these results it is clear that addition of unsubstituted phenylphosphine ligands, in particular the bidentate ligands dppp, dppdmp and dppdep, to either a source of Pd(II) or Pd(0) yields the most active and selective catalysts for the allylation of phenols.

8.2.3 Allylation of other nucleophiles

Apart from 4-*tert*-butylphenol, other nucleophiles have been explored for their reactivity in the presence of the $Pd(OAc)_2$ with dppdmp and the results are summarized in Table 8.4. The aliphatic alcohol 1-octanol is efficiently allylated (Table 8.4; entry 1), while the secondary alcohol cyclohexanol is much less reactive (entry 2); only low conversion towards the allyl ether is observed. Not only alcohols are readily allylated, but also nitrogen-containing substrates such as aniline can be efficiently allylated with allyl alcohol. After 20 hours, conversion is complete when an excess of allyl alcohol is used and mainly the N,N-bisallylated product is obtained (entry 3). After 3 hours the conversion already is quite high, and mostly monoallylated aniline is present (entry 4). The high conversion after only 3 hours is illustrative for the much higher reactivity of aniline compared to hydroxyl-containing substrates, which need considerably longer reaction times to achieve similar conversions. By reducing the amount of allyl alcohol, N-monoallylated aniline is formed selectively, although the conversion is considerably lower (entry 5). Finally, apart from aromatic amines, also alkylamines can be allylated, as shown for *n*-octylamine, which is less reactive than aniline (entry 6).

Table 8.4. Reaction of nucleophilic substrates with allyl alcohol (2) catalyzed by Pd –diphosphine complexes [a]



entry	reaction	nucleophilic substrate	reaction time	conversion of **7-8** or **11-12** (%)	selectivity in reaction II (%)	
					13-14	**15-16**
1	I	1-octanol	20	94	-	-
2	I	cyclohexanol	20	11	-	-
3	II	aniline	20	100	25	75
4	II	aniline	3	85	77	23
5[b]	II	aniline	3	16	100	0
6	II	*n*-octylamine	20	81	75	25

[a] Reaction conditions: ratio substrate/allyl alcohol/$Pd(OAc)_2$/dppdmp = 1000/2000/1/4, toluene, 100 °C.
[b] ratio substrate/allyl alcohol/$Pd(OAc)_2$/dppdmp = 1000/500/1/4.

8.2.4 Homogeneous complexes vs heterogeneous nanoparticles

When using zero-valent transition metal complexes as catalysts, the question arises whether the active catalyst is truly a homogeneous metal complex or whether catalytic activity is caused by the formation of heterogeneous nanoparticles or clusters. Especially in the case of Pd(0) catalysts this should be investigated, since numerous reactions have been reported to be catalyzed by heterogeneous nanoparticles, such as hydrogenation,[19] Heck-reactions[20,21] as well as allylic alkylations.[20,21]

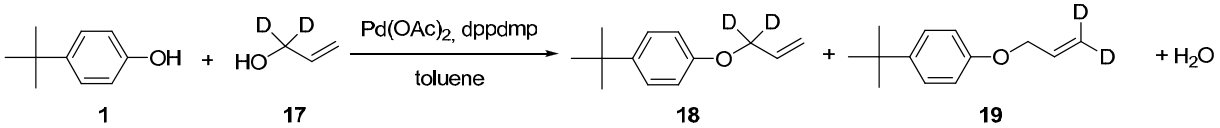
The strong effect of the ligand on the activity and selectivity of the palladium catalysts as described above indicates that a homogeneous complex is responsible for catalytic activity, although ligand-dependent nanoparticle formation cannot be excluded. The use of heterogeneous Pd(0) on carbon as the catalyst does not result in conversion of allyl alcohol, giving another indication that a homogeneous complex is the active catalyst. Finally, when mercury is added to the reaction mixture after one hour, the catalytic system remains active, indicating that truly a homogeneous catalyst is responsible for the observed catalytic activity. The addition of mercury is often used to indicate the presence of active heterogeneous Pd(0) particles, as it leads to the formation of an amalgam with the surface of a heterogeneous catalyst, thereby blocking any catalytic activity.[22]

8.2.5 Mechanistic considerations

The excess of bidentate phosphine ligand (4 equivalents on Pd; 8 equivalents of P on Pd) added to the reaction mixture is necessary to prevent plating of metallic palladium, which leads to loss and therefore deactivation of the catalyst. One equivalent of bidentate phosphine ligand is consumed in the reduction of $Pd(II)(OAc)_2$ to the active Pd(0) species and one bidentate ligand is present on the Pd centre throughout the catalytic cycle. This means that the remaining two equivalents of bidentate ligand will assist in keeping the Pd(0) species in the homogeneous phase when allyl alcohol, diallyl ether or allyl phenyl ether are not coordinated, forming most likely a tetrakisphosphine palladium(0) compound. Allylation of the phosphine groups can occur, but it has been reported to be a reversible process in the presence of Pd(0) catalysts.[23,24] For the reactions with $Pd(dba)_2$ as catalyst precursor, a Pd(0) species is already present and consumption of a phosphine ligand for activation does not take place. The phosphine ligands replace the dba ligands, and one phosphine ligand then needs to be replaced by allyl alcohol to form the active Pd(0) catalyst.

Several mechanisms have been proposed for allylation reactions with allyl alcohol as the allylating agent.[6-8] The formation of an initial Pd(II)(σ-allyl) species is proposed immediately after oxidative addition of allyl alcohol, which rapidly isomerises to a π-allyl species with either phosphine or anion dissociation to maintain a stable 16 e Pd(II) species, depending on the chelate stability of the bidentate phosphine ligand. It has been reported that σ-allyl species are indeed formed in the presence of phosphines and coordinating anions.[24] In order to investigate if a π-allyl species is present at some point in the catalytic cycle, the reaction of **1** was performed with allyl-1,1-d_2 alcohol **17** (Scheme 8.1). This resulted in an approximate 1/1 mixture of allyl-1,1-d_2 4-*tert*-butylphenyl ether and allyl-3,3-d_2 4-*tert*-butylphenyl ether (Scheme 8.1; products **18** and **19**). The observation of scrambling in formation of the deuterated allyl products indicates that a metal π-allyl species must be present somewhere in the catalytic cycle. The dissociation of a phosphine moiety is also believed to play a key role in the mechanism: a strong ligand-structure effect is observed and especially the use of phosphine ligands that do not form kinetically stable chelates on Pd(II), in this case dppb and monodentate triphenylphosphine, results in lower selectivity for O-allylation. In analogy with the Ru-based catalytic system reported in the previous chapter, it is proposed that (at least partial) dissociation of one phosphine moiety of the di-phosphine is needed to accommodate the transition state for intramolecular attack of o-CH moiety of the phenolate by the allyl fragment, and thus for C-allylation to occur. The proposed catalytic cycle is shown in Scheme 8.2.

After formation of the Pd(0) species by means of phosphine oxidation, allyl alcohol coordinates to form species **A**. It is thought that despite the use of excess of (di-)phosphine over Pd, the active organo-Pd species will contain one chelating di-phoshine ligand. Although bis-(bi-dentate phosphine) Pd(0) complexes will certainly exist as resting states, the pseudo zero-order kinetics in ligand concentration suggests that in the applied ligand to Pd ratio of 1-4 and large excess of the allylic substrate, one diphosphine is easily displaced by the allylic substrate, thus reflecting the relatively high "back donation" binding energy of olefin (relative to that of a phosphine moiety) to Pd(0) species. Dissociation of the first di-phosphine

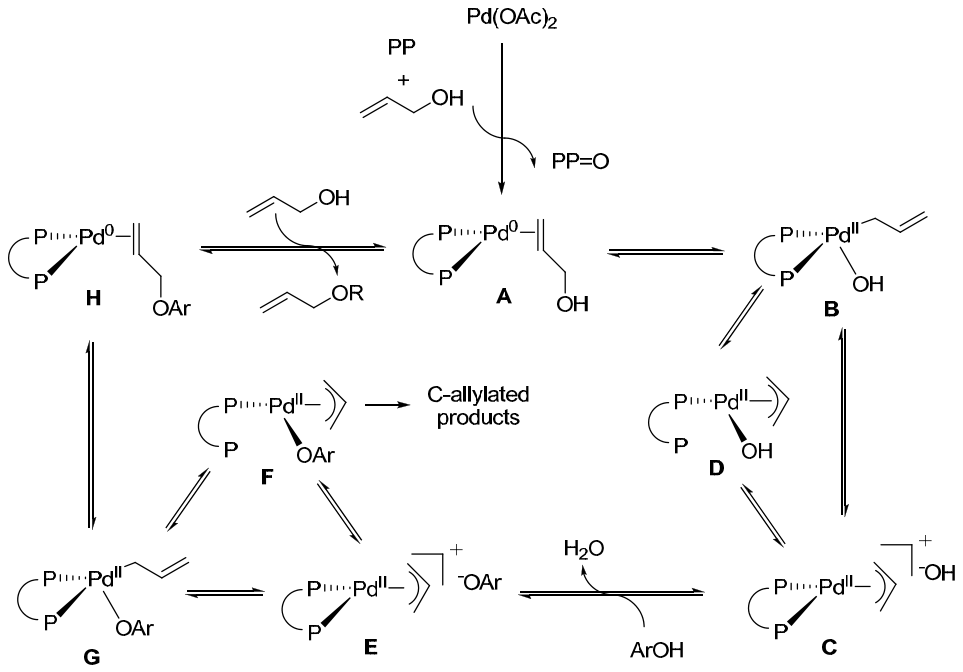


Scheme 8.1. Reaction of **1** with deuterated allyl alcohol **12** in the presence of a Pd(PP) catalyst.

ligand is expected to be much less energy demanding than dissociation of the single remaining di-phosphine ligand at Pd.

Oxidative addition takes place to initially form the σ-allyl Pd(II) species **B**, which is in equilibrium with the isomeric π-allyl intermediates **C** and **D**. Due to exchange of the anion via an acid-base reaction, the phenolate Pd(II) species **E**, **F** and **G** are formed. The reductive elimination towards O-allylated products is believed to take place from intermediate **G**, in agreement with the Tsuji-Trost mechanism, in which it is proposed that hard nucleophiles, such as phenolate, coordinate to the metal centre prior to reductive elimination.[5] After this step, an intermediate in which the allyl phenyl ether product is bound to Pd(0), (**H**) is formed. As indicated, C-allylated products are most likely formed via a (mono)phosphine dissociation step (**F**). Finally, the product is replaced with a molecule of allyl alcohol to complete the catalytic cycle.

The catalysts with the highest selectivity have ligands with C_3-based bridging groups, being dppp, dppdmp and dppdep, for which stable chelation is expected in the Pd(II) intermediates **E** and **G**. This is most likely caused by the fact that the natural bite angle of these ligands is close to 90°, which is also the optimal angle required for cis-coordination in a square-planar Pd(II) complex, making the chelate ring free of strain and relatively stable under the reaction conditions. The introduction of alkyl substituents at C_2 of the C_3-bridging group of the ligand is less important for selectivity, as the unsubstituted dppp ligand already gives highly selective O-allylation. Note, however that bulkier di-Et C_2–backbone substituents yield a small but measurably higher selectivity for O-allylation. However, more distinctly, the stability of the complex improves by the use of *gem*-dialkyl substituted ligands. Deactivation via plating to Pd-black will be related to phosphine dissociation of the ligand and thus due to a more stable chelation, catalyst deactivation is prevented. The ligands which create a large P-Pd-P angle (> 90°), such as dppb or two monodentate PPh_3 ligands, result in a catalyst with a relatively low selectivity. Since the P-Pd-P angle deviates from the preferred 90°, chelation of this type of ligands is weaker than that of ligands with C_3-based bridging groups. Intermediate most likely **F** is lower in energy and will be more abundant. C-allylation requires sufficient coordination space on the Pd(II)(allyl) intermediate in order to activate the *ortho*-position of the phenolate-anion and in species **F** this space is provided.



Scheme 8.2. Proposed mechanism for Pd-catalyzed allylation of phenols.

Addition of acid at any time during the reaction immediately inhibits the allylation reaction. It has been reported that Pd(II)-hydride species are formed from a Pd(0) species and *p*-toluenesulfonic acid;[25] this would prevent the catalyst to return to the Pd(0) state, which is the active species.

A unique feature of the Pd catalysts is the benefit that even considerably stronger nucleophiles (than alcohols), such as primary and secondary amines, can also be efficiently allylated. This again can be seen as a consequence of the strong (back donating) binding energy of the olefinic moiety of allyl alcohol to Pd(0), relative to that of the N-coordination of amines. This allows an easy approach of allyl alcohol to the Pd(0) centre without much competition by the nitrogen compound. In fact, strong nitrogen coordination is thought to be the reason why strongly Lewis acidic cationic Ru catalysts, as reported in the previous chapters, are unsuitable for allylation of amines: strong coordination compounds between Ru and the basic amine exist.

8.3 Conclusions

Pd-phosphine complexes show good catalytic activity in allylation reactions with allyl alcohol as the allylating agent in the absence of additives. Complexes with a chelating phosphine ligand with C_3-based bridging groups show high selectivity towards O-allylation of phenols. Introduction of *gem*-dialkyl substituents on C_2 of ligand backbone results in an increase of

the conversion of the reaction, most likely due to an enhanced stability of the Pd(0) species. The use of diallyl ether as allylating agent results in an increase in the conversion while maintaining the high selectivity for O-allylation. Both $Pd(II)(OAc)_2$ as well as $Pd(0)(dba)_2$ can be used as catalyst precursor in combination with phosphine ligands. Catalysts having phosphine ligands with non-substituted phenyl rings show higher activity compared to catalysts with phosphine ligands with *ortho*-methoxy substituted phenyl rings, possibly due to coordination of the methoxy groups. Apart from 4-*tert*-butylphenol, also aliphatic alcohols are efficiently allylated, as well as aromatic or aliphatic amines.

8.4 Experimental

General remarks. All reactions were performed under an argon atmosphere using standard Schlenk techniques. Solvents were dried and distilled using standard procedures and were stored under argon. The phosphine ligands with phenyl substituents (dppm, dppe, dppp, dppb and PPh_3) and triphenylphosphite were commercially available and used as received. $Pd(OAc)_2$ and $Pd(dba)_2$ were purchased from Strem Chemicals. The ligands dppdmp,[26] dppdep,[27] *o*-MeOdppp,[28] *o*-MeOdppdmp,[29] *p*-MeOdppp,[30] *o*-Medppp[31] and trisanisylphosphine[32] were earlier described in literature. The compounds **3**-**6**, allyl 1-octyl ether, allyl cyclohexyl ether, allyl-1,1-d_2 4-tert-butylphenyl ether and allyl-3,3-d_2 4-tert-butylphenyl ether were reported in previous chapters. The spectroscopic data of N-allylaniline, N,N-diallylaniline, N-allyloctan-1-amine and N,N-diallyloctan-1-amine corresponded with the data reported in literature.[33]

General procedure for catalytic reactions with $Pd(OAc)_2$. 5 mmol of 4-*tert*-butylphenol (or an aliphatic alcohol or an amine), 5 μmol of $Pd(OAc)_2$ and 20 μmol of bidentate phosphine ligand (or 40 μmol of PPh_3) were charged into the reaction vessel which was then flushed with argon (unless stated otherwise). Degassed and dried toluene or heptane (5 ml) was added and the mixture was stirred for 5 minutes. The allyl donor was added and the reaction mixture was heated to 100 °C. Samples were taken at certain time intervals and were analyzed by gas chromatography.

General procedure for catalytic reactions with $Pd(dba)_2$. 5 mmol of 4-*tert*-butylphenol, 5 μmol of $Pd(dba)_2$ and 20 μmol of phosphine bidentate ligand (or 40 μmol of monodentate ligand) were charged into the reaction vessel which was then flushed with argon (unless stated otherwise). Degassed and dried toluene (5 ml) was added and the mixture was stirred for 5 minutes. Allyl alcohol was added and the reaction mixture was heated to 100 °C. Samples were taken at certain time intervals and analyzed by gas chromatography.

Procedure for mercury test. The general procedure for catalytic reactions with $Pd(OAc)_2$ was followed with the difference that after one hour reaction time, 100 mg (0.5 mmol) of mercury was added. The reaction mixture was stirred vigorously and the reaction was continued at a temperature of 100 °C. Stirring was temporarily halted while taking samples to prevent sampling of mercury droplets.

8.5 References

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9

Selective O-allylation of bisphenol A: the ultimate goal

Abstract
The O-allylation of bisphenol A is attempted with the most selective catalysts for O-allylation of phenols reported in the previous chapters. Both ruthenium as well as palladium catalysts are capable of selectively performing single and double O-allylation. The choice of the solvent is of key importance and the use of an excess of diallyl ether results in relatively high yields for the bisallyl ether of bisphenol A, while maintaining high selectivity for O-allylation.

9.1 Introduction

Multiple allylations of BPA have been reported in literature, but these studies do not make use of allyl alcohol (or diallyl ether), but either allyl halides,[1-5] allyl acetates,[6,7] or allyl carbonates[8] are employed as the allylating agent. A stoichiometric amount of base is also often employed to create phenolate anions *in situ*, increasing the nucleophilicity on the O-position.

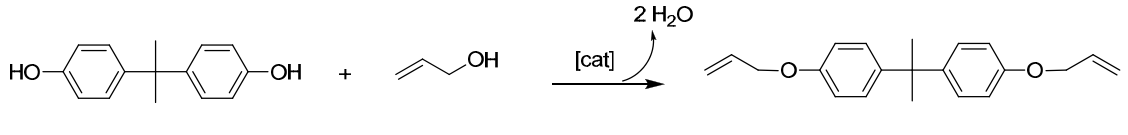
In the previous chapters, the detailed study of mono-O-allylation of phenols was reported. 4-*Tert*-butylphenol was mainly used as a model substrate for bisphenol A (BPA), in order to simplify the analysis of the multiple products that can be formed. The investigation has led to a better understanding of the mechanism for O-allylation of phenols with allyl alcohol and revealed the requirements for a suitable catalyst and optimal reaction conditions. Several very selective catalytic systems were found for O-allylation of phenols, like [RuCp(dppb)](OTs) (Chapter 2) and [RuCp(PPh_3)$_2$](OTs) (Chapter 4) in the presence of acid, the immobilized [RuCp(PPh_3)(resinPhPPh_2](OTs) in the presence of acid (Chapter 6) and $Pd(OAc)_2$ with dppdmp as the ligand (Chapter 8). Having several options in hand for the selective O-allylation of a monophenol with allyl alcohol into an allyl phenyl ether, BPA was used as the ultimate substrate.

The goal is to perform a double O-allylation as was proposed in the introduction of this thesis (Scheme 9.1). The main problem arising from using BPA as a substrate is that a large number of different of products can be formed (Scheme 9.2). Whereas in the allylation of 4-*tert*-butylphenol a total of four products are observed, in the allylation of BPA a total of fourteen different products can theoretically be obtained, increasing the importance of the use of highly selective catalysts.

9.2 Results and discussion

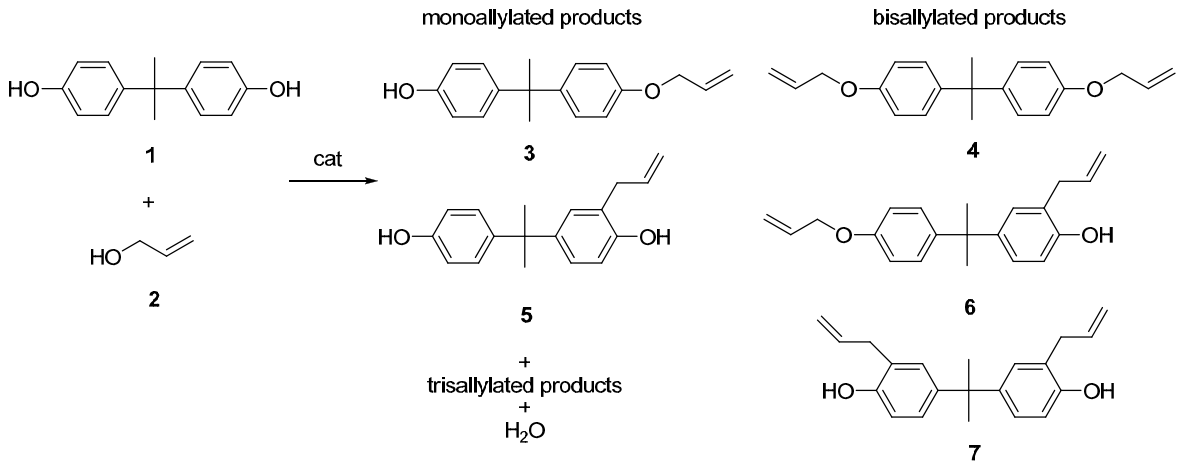
9.2.1 Product analysis

Apart from the increase of possible products when 4-*tert*-butylphenol was replaced with BPA, also the analytical method used to quantify the product formation has to be changed.



1 2 4

Scheme 9.1. Proposed chlorine-free and salt-free process towards synthesis of bisglycidyl bisphenyl A ether.



Scheme 9.2. Structures of mono- and bisallylated products **3**-**7** formed in allylation of BPA with allyl alcohol. Structures of trisallylated products are not shown.

Detection with GC was not possible and HPLC was used to quantify the product formation. Products **3**-**7** are efficiently separated by means of HPLC and characterized with LC/MS. The O-allylated product **3** and **4** were also synthesized by reported procedures,[4] characterized by NMR spectroscopy and LC/MS. Response factors in UV-detection proved to be independent of the allylic substitution. The phenol moieties are initially monoallylated, either O- or C-allylation, before one of the rings is substituted with a second allyl moiety, which only occurs after longer reaction times. This product development is observed for all the allylation reaction with BPA. The trisallylated products are only present in very low concentrations for the less selective reactions. These products could not be separated efficiently. The selectivity for O-allylation is defined by calculating the percentage of O-allylated products (**3** + **4**; Scheme 9.2) on the total amounts of products formed.

9.2.2 Catalytic allylation of BPA

The selection of the most selective catalyst found during this research project and their reactivity in the O-allylation of BPA with allyl alcohol is shown in Table 9.1. The ratio BPA over catalyst used was 500/1 and therefore conversions of **1** (Scheme 9.2) after one hour are higher compared to the reactions with 4-*tert*-butylphenol reported previously, where a substrate over catalyst ratio of 1000/1 was generally used. However, when the number of OH-moieties is considered, conversions of 4-*tert*-butylphenol and BPA are similar. $[RuCp(PPh_3)_2](OTs)$ in the presence of acid (*p*-toluenesulfonic acid = HOTs) shows to be reasonably selective for O-allylation of BPA with a conversion of 46% of BPA and a selectivity of 80% for O-allylation (entry 1). However, when compared to the selectivity for O-allylation of 4-*tert*-butylphenol (>90%), this selectivity is considerably lower. The lower selectivity towards O-allylation is most likely caused by the fact that product **4** is formed after

Table 9.1. Allylation of BPA using several catalytic systems and conditions [a]

entry	catalytic system	allylating agent	temperature (°C)	conversion of **1** (%) and selectivity for O-allylation (%)[b]		yield of **4** after 3 h (%)
				1 h	3 h	
1	$[RuCp(PPh_3)_2](OTs)$	allyl alcohol	60	46 (80)	46 (63)	14
2	$[RuCp(PPh_3)_2](OTs)$	diallyl ether	60	91 (68)	98 (48)	30
3	$[RuCp(PPh_3)_2](OTs)$	allyl acetate	60	81 (74)	90 (52)	18
4[c]	$[RuCp(PPh_3)_2](OTs)$	allyl alcohol	60	22 (70)	31(50)	5
5	[RuCp(dppb)](OTs)	allyl alcohol	80	62 (66)	89 (65)	20
6[d]	$[RuCp(PPh_3)(resinPhPPh_2](OTs)$	allyl alcohol	80	80 (80)	81 (76)	25
7[e]	$Pd(OAc)_2$ + dppdmp	allyl alcohol	100	38 (100)	54 (100)	10

[a] Reaction conditions: ratio BPA/allyl alcohol/[Ru]/AgOTs/HOTs = 500/2000/1/2/20, toluene.
[b] Selectivity towards O-allylation indicated in parentheses. O-allylation = **3** + **4**; C-allylation = **5**-**7** + trisallylated compounds.
[c] *n*-heptane was used as solvent
[d] Reaction conditions: ratio BPA/allyl alcohol/[Ru]/AgOTs/HOTs = 50/200/1/2/2, toluene.
[e] Reaction conditions: ratio BPA/allyl alcohol/$Pd(OAc)_2$/dppdmp = 500/2000/1/4, 100 °C.

two equilibrium reactions and therefore less likely to form compared to a mono-O-allylated phenol.

When allyl alcohol is replaced with diallyl ether as the allylating agent, conversions are higher (entry 2). C-allylation commences at an earlier stage during the reaction, due to the higher initial conversion, since diallyl ether formation from allyl alcohol is not occurring. If allyl acetate is used as the allylating agent (entry 3), the reaction is only active in the presence of *p*-toluenesulfonic acid, most likely to form acetic acid and thus preventing formation of the relatively strong coordination acetate anion. With the use of allyl acetate, allylating agent of choice in patents of Dow Chemicals,[6,7] selectivity for O-allylation is not increased. For reactions reported in these patents $[RuCpCl(PPh_3)_2]$ is used as the catalyst, but selectivity is not reported in a clear manner and a very high catalyst concentration is used (2 mol%). When such an experiment is reproduced (for exact procedure see experimental part), selectivity for O-allylation is low (41%) and a large amount of trisallylated product is obtained (52%). The use of allyl acetate does not lead to more selective reactions and allyl alcohol or diallyl ether remain the choice for more attractive allylating agents. The use of *n*-heptane as a solvent gives significantly lower conversions and selectivity (entry 4) compared to toluene. This can be explained by the low solubility of BPA in *n*-heptane at the reaction temperature. The desired products (**3** + **4**) however, are soluble and therefore the reaction of these products into the undesired C-allylated products is faster than the O-allylation of **1**. The use of [RuCp(dppb)](OTs) as the catalyst (entry 5), gave low selectivity, but this catalyst was somewhat more selective compared to the $[RuCp(PPh_3)_2](OTs)$ after 3 hours reaction time with high conversion. The use of the immobilized Ru-catalyst (entry 6) gave a highly

selective reaction towards O-allylation and the catalyst was effectively recovered (leaching was 1.0 % of total Ru-content on support). Finally, $Pd(OAc)_2$ in combination with the dppdmp ligand gave excellent selectivity towards O-allylation (entry 7), but after three hours, mainly product **3** was formed and only 10% of the bisallyl ether **4** is obtained.

The equilibrium reaction of O-allylation is controlled by the amount of water that dissolves in the organic phase. Toluene is beneficial to obtain a reasonable conversion; it is quite apolar so that water solubility in the reaction medium is low, but it is not too apolar for BPA to dissolve at reaction temperature. An extra benefit from using toluene is that the desired product is completely soluble at room temperature, while the starting material BPA is not and conveniently crystallizes from the reaction mixture in high purity.

9.2.3 Allylating agents as solvent

The reaction with $[RuCp(PPh_3)_2](OTs)$ as the catalyst in the presence of acid and with diallyl ether as the allylating agent gave the highest yield of **4** (30% after 3 hours). Selectivity for O-allylation is however not very high and a large amount of C-allylated products are formed. In an attempt to improve the selectivity of the reaction, different solvent systems were investigated and the results are shown in Table 9.2.

When the reaction is performed in allyl alcohol as the solvent, no conversion of **1** is observed (entry 1) and only formation of diallyl ether is detected. With diallyl ether as the solvent (entry 2), the reaction proceeds very selective towards O-allylation, but mainly product **3** is

Table 9.2. Allylation of BPA in the presence of Ru- or Pd-based catalysts with different solvent systems [a]

entry	catalyst	solvent	conversion of **1** (%) and selectivity for O-allylation (%)[b]		yield of **4** after 3 h (%)
			1 h	3 h	
1	$[RuCp(PPh_3)_2]^+$	allyl alcohol	0 (-)	0 (-)	0
2	$[RuCp(PPh_3)_2]^+$	diallyl ether (DAE)	47 (100)	54 (94)	9
3	$[RuCp(PPh_3)_2]^+$	DAE / toluene = 2/1	86 (85)	95 (82)	50
4	$[RuCp(PPh_3)_2]^+$	DAE / toluene = 1/1	95 (81)	95 (72)	51
5	$[RuCp(PPh_3)_2]^+$	DAE / toluene = 1/2	96 (68)	96 (64)	46
6	$[RuCp(PPh_3)_2]^+$	DAE / heptane = 2/1	55 (91)	80 (86)	23
7	$[RuCp(PPh_3)_2]^+$	DAE / heptane = 3/1	80 (92)	98 (84)	49
8	$[RuCp(PPh_3)_2]^+$	DAE / heptane = 4/1	78 (93)	90 (88)	38
9[c]	$Pd(OAc)_2$ + dppdmp	DAE / toluene = 2/1	12 (100)	28 (100)	2 (24)

[a] Reaction conditions: ratio BPA/allyl alcohol/$[RuCpCl(PPh_3)_2]$/AgOTs/HOTs = 500/2000/1/2/20, 60 °C, total solvent volume = 2.5 ml

[b] Selectivity towards O-allylation indicated in brackets. O-allylation = **3** + **4**; C-allylation = **5**-**7** + trisallylated compounds.

[c] Reaction conditions: ratio BPA/allyl alcohol/$Pd(OAc)_2$/dppdmp = 500/2000/1/4, 100 °C, total solvent volume = 2.5 ml. Yield of **4** in parentheses determined after 20 hours reaction time. Selectivity for O-allylation remains 100%.

formed and only 9% of **4** is formed after 3 hours reaction time. When the solvent is made more apolar by using a mixture of diallyl ether and toluene (entry 3), conversion of **1** and yield of **4** is increased in a major way and 50% of **4** (based on **1**) is formed, a very high yield for a product formed via two equilibrium reactions. Making the solvent more apolar by increasing the amount of toluene on diallyl ether causes selectivity to decrease (entry 4 and 5). Apart from toluene as the apolar component in the reaction mixture, also *n*-heptane can be used. When the results from entries 6-8 are compared to that of entry 3, slightly less *n*-heptane than toluene should be used for a optimal selectivity for O-allylation. This is obviously caused by the higher apolarity of *n*-heptane than that of toluene. Finally, besides the $[RuCp(PPh_3)_2]^+$ catalyst, the Pd-catalytic system proved to be highly selective for O-allylation. When a diallyl ether / toluene mixture is used as the solvent, the reaction is completely selective for O-allylation, however, conversion of **1** after 3 hours is considerably lower than that of the Ru-based catalytic system. After 20 hours, only O-allylated products are detected while the yield for **4** increases to 24% based on **1**. Even longer reaction times did not result in higher conversion, indicating complete deactivation of the catalyst.

9.2.4 Industrial application

When the allylation reaction described above with BPA as the substrate is implemented in an industrial process, several things should be noted. Due to the thermodynamical preference of C-allylation over O-allylation of phenols, the reaction will eventually build up C-allylated side products, of which the concentration depends on a combination of catalyst structure and reaction time and is independent on allylating agent. It is therefore of key importance that the reaction is halted before C-allylated products form when performed in a batch reaction. In a continuous process, both water, forming a separate phase in the reaction mixture, and the desired product needs to be efficiently removed from the reaction mixture while feeding it with new starting materials. The very low polarity of product **4** compared to **1** and water could be used to separate these compounds by extraction. Diallyl ether should be used as (co-) solvent, which can be efficiently synthesized from allyl alcohol. With the use of $[RuCp(PPh_3)_2](OTs)$ + HOTs as the catalytic system, extremely high turnover number can be achieved based on allyl alcohol (> 200,000), as was already demonstrated in Chapter 4.

9.3 Conclusions

$[RuCp(PPh_3)_2](OTs)$ in the presence of acid is very selective for O-allylation of BPA and high yields (~50%) of the bisallyl ether of BPA are obtained. Allyl alcohol or diallyl ether perform equally well or better compared to allyl acetate as allylating agent. The choice of solvent is crucial for both high conversion as well as high selectivity for O-allylation. Diallyl ether seems to be the allylating agent of choice for reaction with BPA and is best used as solvent in the presence of an apolar co-solvent, like toluene or *n*-heptane. $Pd(OAc)_2$ with the phosphine ligand dppdmp as catalyst is even more selective compared to the Ru-based system. C-allylated products are not detected, even after longer reaction times. Catalyst stability is however the bottleneck when using this catalyst, as was already discussed in Chapter 8.
The atom-efficiency of this catalytic reaction, is much higher compared to the conventional saline reaction, where a phenolate salt is reacted with an allyl halide. However, for industrial application, the catalytic reaction, being a double equilibrium reaction with a maximum yield of 50%, is at this stage of development much more difficult to perform to compared to the conventional saline reaction, giving nearly quantitative yields.

9.4 Experimental

General remarks. All reactions were performed under an argon atmosphere using standard Schlenk techniques. Solvents were dried and distilled by standard procedures and stored under argon. Bisphenol A was obtained as a gift from Hexion Speciality Chemicals and used as received. Procedures for catalysts syntheses have been reported in the previous chapters.

General procedure for catalytic reactions with Ru-catalysts. 1.25 mmol of BPA, 2.5 μmol of Ru-complex, 5.0 μmol of AgOTs and 0.05 mmol HOTs were charged into the reaction vessel and flushed with argon. Degassed and dried toluene or *n*-heptane (2.5 ml, unless stated otherwise) was added and the mixture was stirred for 5 minutes. The allyl donor was added and the reaction mixture was heated to reaction temperature. Samples were taken at certain time intervals and analyzed by HPLC.

Procedure for catalytic reactions with Pd-catalyst. 1.25 mmol of BPA, 2.5 μmol of $Pd(OAc)_2$ and 10 μmol of dppdmp were charged into the reaction vessel and flushed with argon. Degassed and dried toluene (2.5 ml; unless stated otherwise) was added and the mixture was stirred for 5 minutes. The allyl donor was added and the reaction mixture was heated to reaction temperature. Samples were taken at certain time intervals and analyzed by HPLC.

Procedure of Dow patent reaction. A mixture of 285 mg (1.25 mmol) BPA, 36 mg $[RuCpCl(PPh_3)_2]$ (2 mol%) and 2.5 g (25 mmol) allyl acetate under an argon atmosphere is stirred at 95 °C. After 6 hours, the mixture was analyzed by HPLC.

HPLC analysis. HPLC analysis was performed with a Summit Dual Gradient HPLC system (Dionex) connected with a PDA3000 diode array detector (Dionex). The HPLC was equipped with an Alltima HP C18 3u reverse phase column (150x4.6 mm), with a flow of 1 ml/min and injection volume of 10 µl of a solution of the reaction mixture in acetonitrile. The gradient conditions were at t = 0-17 (minutes) acetonitrile (%) / water (%) = 50/50, t = 17-23 acetonitrile 100%, t = 23-30 acetonitrile (%) / water (%) = 50 / 50. Spectroscopic data for **3**-**7** corresponded with that reported in literature.[1]

9.5 References

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10

Summary, conclusions and outlook

10.1 Summary

10.1.1 Introduction

The current production of epoxy resin components employs chloride-containing reagents and produces highly polluting chloride-containing byproducts and salt waste in stoichiometric amounts. For the development of a chloride-free route towards epoxy resins, O-allylation of phenols, in particular bisphenol A, is highly desired. Most types of allylation reaction use allyl donors with good leaving groups like halides or acetates. Such a reaction would still produce salt waste and therefore allyl alcohol is, from an environmental point of view, a much more desirable allylating agent, since only water is produced as byproduct. A major drawback for the use of allyl alcohol is its low reactivity in allylations compared to allyl halides or acetates. Catalytic allylation reactions of phenols using allyl alcohol as the allylating agent are described in literature, however, until now, a stoichiometric amount of base needs to be added to selectively perform O-allylation and prevent C-allylation.
In chapter 1, various types of allylation reactions are discussed and compared, both for allyl donors with good leaving groups, as well as allyl alcohol. An emphasis on $[RuCp(PP)]^+$ catalysts is made and the properties of phosphine ligands is discussed in depth.

10.1.2 $[RuCp(PP)]^+$ complexes in allylation of phenols with allyl alcohol as allylating agent

A new catalytic method has been investigated to obtain either O- or C-allylated phenolic products using allyl alcohol or diallyl ether as the allyl donor without the need of any stoichiometric amounts of additives. With the use of $[RuCp(PP)]^+$-catalysts described in Chapter 2, both O- and C-allylation are found to occur. It is shown that the O-allylated products are reversibly formed, while C-allylated products are produced irreversibly and therefore, the selectivity of the reaction is time-dependent. It has been demonstrated that a Ru-catalyzed conversion of O-allylated products to the thermodynamically more favorable C-allylated products may readily occur under allylation conditions. The structure of the bidentate ligand, however, has a major influence on catalytic activity as well as chemoselectivity. In addition, a strong cocatalytic effect of small amounts of acid is revealed. It is proposed that protons strongly reduce the activation barriers for oxidative addition and reductive elimination at the RuCp(PP) centre, for both of the substrate allyl alcohol as well as product allyl ether compounds. Restricted coordination space at the ruthenium centre favors the formation of the O-allylated product, while ample space, either due to weak chelation

and/or small bite angle, favors C-allylation. The effect of chelation stability on selectivity of the reaction is investigated and discussed in more depth in the following section.

10.1.3 A gem-dialkyl effect induces high selectivity for O-allylation of phenols with allyl alcohol

Catalysts containing bidentate phosphine ligands having geminal dialkyl substituents at the central atom of a C_3-bridging group of the phosphine ligand are highly selective for O-allylation, as is described in Chapter 3. The thermodynamically favored C-allylation can be efficiently blocked even after long reaction times. It appears that the electronic and structural properties of the Ru(II) precursor complexes in the solid state do not differ significantly from those of complexes containing unsubstituted analogous ligands, while the resulting catalysts show a vastly different catalytic performance. The results point to the fact that the geminal dialkyl substitution at the central carbon of the C_3 bridge of the ligand leads to an increased kinetic stability of the bidentate chelate under reaction conditions. The cause of the kinetically stable chelating properties of these ligands is due to a reduced rotational freedom of the ligands. Therefore entropy gain on dissociation is low, which causes the ligand to remain coordinated onto ruthenium, thus inducing high selectivity towards O-allylation. The rigidity of the ligand is also expected to hinder oxidative addition of allyl donors at Ru(II), which is considered to be the rate-determining step, explaining the relatively lower activity of complexes with *geminal* substituted C_3-bridging ligands. The results provide a very interesting example in which the application of the geminal dialkyl substitution in the bridge of a bidentate ligand serves as a diagnostic tool to probe the nature of the selectivity-determining step in a catalytic pathway in homogeneous catalysis.

10.1.4 Switchable catalysis between isomerization and allylation tuned by addition of acid

In Chapter 4, it is reported that the highly active allyl alcohol redox isomerization catalyst $[RuCp(PPh_3)_2](OTs)$ upon addition of a catalytic amount of a strong acid changes its catalytic action to the O-allylation of phenols with allyl alcohol. High turnover numbers (75,000 based on phenol; 200,000 based on allyl alcohol) are reached and the catalyst is very stable in the presence of substrate. The stability decreases with the decreasing concentration of substrate at high conversion, where catalyst deactivation is observed. Addition of triphenylphosphine to the reaction mixture does not lead to further stabilization of the catalyst; instead the free phosphine is rapidly allylated and allyl phosphonium salts are formed. In this reaction the acid

is consumed, which deactivates the catalytic system for allylation reactions. Coordinated triphenylphosphine, however, is not susceptible for allylation, which indicates that the triphenylphosphine attacks the allyl species from outside the coordination sphere of the catalyst. This catalyst with monodentate phosphine ligands is superior both in activity and selectivity to similar catalysts with bidentate phosphine ligands. Apart from phenols, also thiophenol can be efficiently allylated. A more elaborate exploration of the scope of possible substrates is described in the next paragraph.

10.1.5 Exploring the scope of the allylation reaction catalyzed by [RuCp(PP)]$^+$-complexes

In Chapter 5, the scope of the allylation reaction discussed in the previous chapters is explored. It is shown that apart from phenols, primary, secondary and even tertiary aliphatic alcohols can be successfully allylated with allyl alcohol or even with diallyl ether as the allylating agent, obtaining a high yield for the alkyl allyl ether. The reactivity of aliphatic alcohols is in the order of primary > secondary >> tertiary. The preference for an alkyl allyl ether over a diallyl ether has a thermodynamic origin, which explains the high selectivity for the alkyl allyl ether and high conversion of the aliphatic alcohol. Apart from alcohols as nucleophilic substrates, also thiols, both aromatic and aliphatic, and indole are efficiently allylated. However, aniline acts as a catalyst inhibitor. Substituted allylic alcohols with a terminal olefin moiety as allylation agents have a higher reactivity than allylic alcohols with an internal olefin moiety. Of the latter, (*Z*)-allylic alcohols are considerably more reactive than (*E*)-allylic alcohols. The regio-structure of the substituted allyl alkoxy-moiety in the product ether remains predominantly the same as in the allylic alcohol allylation agent, indicative of a slow σ-π allyl-rearrangement relative to the product reductive eliminating step at the Ru(IV) intermediate.

10.1.6 Immobilization of [RuCp(PP)]$^+$ complexes and their activity in allylation reactions

[RuCp(PP)]$^+$ complexes that have been demonstrated to be active in the homogeneous liquid phase for allylation of alcohols with allyl alcohol as the allylating agent, were immobilized onto solid supports, as reported in Chapter 6. Two different methods are used for this immobilization: (1) via electrostatic interactions on ion-exchange resins, where the anion is fixed on the support, and (2) via a coordination bond, where a ligand is covalently bound on the support. Both methods give high yields of immobilized complex through relatively simple procedures. The catalysts immobilized via ionic interactions prove to be able to allylate both

1-octanol and 4-*tert*-butylphenol with very low leaching of the catalyst, although the phenol was very selectively C-allylated instead of O-allylated. Due to the hydrophilicity of these resins, however, water is retained in the resin, which is detrimental for O-allylation of phenol. The immobilization of the ruthenium catalysts by covalent interactions onto supports without hydrophilic residues makes O-allylation possible. Although leaching from the resin is somewhat higher than for the catalyst immobilized on ion-exchange resins, the activity over multiple runs is relatively stable. Quarternisation of the excess of phosphine present on the support plays an important role in the activity of the catalysts for the allylation reaction. The activity, in an absolute sense per Ru centre, of all heterogeneous systems described in this chapter, is significantly lower than that of the homogenous catalysts described earlier.

10.1.7 Theoretical study on the Ru-catalyzed allylation of phenols with allyl alcohol

The two steps in the allylation mechanism which determine activity and selectivity of catalytic allylations reaction with $[RuCp(PP)]^+$ complexes are (i) oxidative addition of the allylation agent and (ii) reductive elimination of the allylated product, respectively. The intermediates, proposed in the previous chapters that play a key role in these steps, are modelled using Density Functional Theory, as is reported in Chapter 7. Calculations were made of the reaction energy profile both in the absence, as well as in the presence of added acid. The energetic effects of changing the chelating phosphine ligand are found both in the oxidative addition step, as well as in the reductive elimination step. Observations made from experiments in previous chapters are supported by the results of the calculations. The incorporation of *gem*-dialkyl C_1-backbone substituted diphosphine ligands in the catalysts stabilizes bidentate phosphine coordination in the Ru(IV) state. This effect reflects the increased basicity of P due to the electron-donating effect of the alkyl substituents. As expected, however, a possibly increase of the binding energy to Ru(IV) of chelating diphosphine ligands with *gem*-dialkyl substition at C_2 of the C_3 backbone is not reflected in the energy calculations. It is concluded that the increased kinetic stability of the bidentate coordination of diphosphines, containing a C_2 substituted C_3 backbone, to Ru(IV), as deduced from the effects on catalytic performance must have an entropic origin, that is not considered in the DFT calculations. The basis of the increased kinetic stability of chelation at Ru(IV) must be seen in the reduced rotational freedom of the substituted backbone ligands that leads to less entropy gain on removing chelation of the ligand by dissociation of one of the phosphine moieties from the metal centre.

10.1.8 Palladium complexes with bidentate phosphine ligands as catalyst for allylation reaction with allyl alcohol

Several palladium complexes with bidentate phosphine ligands were tested for their activity in the O-allylation of phenols with allyl alcohol. The catalytic systems reported in Chapter 8 do not require a drying agent, or stoichiometric amounts of additives, to induce activity. Complexes with a chelating phosphine ligand with C_3-based bridging groups show very high selectivity towards O-allylation of phenols. Introduction of *gem*-dialkyl substituents increases the conversion of the reaction, most likely due to an increase in the stability of the Pd(0) species. The use of diallyl ether as the allylating agent results in a significant increase in conversion without loss of selectivity. Both $Pd(II)(OAc)_2$ as well as $Pd(0)(dba)_2$ as catalyst precursor in combination with phosphine ligands results in the formation of active catalysts. Catalysts with phosphine ligands with non-substituted phenyl rings show higher activity compared to catalyst with phosphine ligands with *ortho*-methoxy substituted phenyl rings, possibly due to coordination of the methoxy groups to the Pd center, thereby hampering approach and coordination of the substrate. With the reported palladium catalytic system not only phenol, but also aliphatic alcohols can be efficiently allylated, as well as aromatic and aliphatic amines.

10.1.9 Bisphenol A as the ultimate substrate in selective O-allylation of phenols

The O-allylation of bisphenol A (BPA) has been performed with the most selective catalysts for O-allylation of phenols reported in the previous chapters. To obtain high selectivity towards O-allylation without stoichiometric additives like bases, the catalyst structure is the determining factor. Both $[RuCp(PPh_3)_2](OTs)$ in the presence of acid and $Pd(OAc)_2$ with the phosphine ligand dppdmp are shown in Chapter 9 to be very selective for O-allylation of BPA. Relatively high yields (~50%) of the bisallyl ether of BPA are obtained. The choice of solvent is crucial for both high conversion as well as high selectivity for O-allylation. The use of an excess of diallyl ether results in good yields for the bisallyl ether of bisphenol A, while maintaining high selectivity for O-allylation.

10.2 Conclusions and outlook

The aim of the research described in this thesis has been to understand how catalytic O-allylation of phenols, ultimately of BPA, with allyl alcohol as allylating agent, can be performed. With mainly 4-*tert*-butylphenol as a model substrate, many types of catalysts were

investigated for their behavior in the allylation reaction. With the use of complexes with *gem*-dialkyl substituted bidentate phosphines, the selectivity-determining step was identified. This type of phosphine ligands can be used in other catalytic reactions to identify key steps in the catalytic cycle. The experimental results have been illustrated by modeling of the catalytic intermediates with DFT calculations. Although several phenomena observed in experiments were supported by these calculations, a more detailed and intensive calculating method should be employed to illustrate other aspects, especially the *gem*-dialkyl effect.

Apart from 4-*tert*-butylphenol, several other types of substrate could be successfully allylated. A challenge would be to perform allylations on more complex substrates. When performed efficiently in the presence of functional groups, elaborate protection/deprotection steps are circumvented, reducing the number of synthetic steps in a total synthesis. Such steps are normally needed to prevent undesired reactions of reagents with functional groups. The reversibility of the allylation reaction makes it possible to protect and deprotect functional groups with the same catalyst and is tuned by using an excess of either allylating agent for protection or water for deprotection. The use of substrates with a suitable allylating agent in their substructure, like glycals (= cyclic enol ethers), should be explored to find new reactivity with such compounds.

The $[RuCp(PPh_3)_2](OTs)$ complex as a highly selective catalyst was surprising, since it has been reported as one of the most efficient catalyst for isomerization of allyl alcohols into carbonyl compounds, as described in Chapter 4. However, a change of reaction conditions makes it a highly efficient catalyst for allylation reactions, showing the strong impact of changing only the acidity of the reaction mixture. Since all of other Ru-based catalysts reported in this thesis are directly synthesized from $[RuCpCl(PPh_3)_2]$, it is a very attractive and relatively cheap catalyst.

No other catalytic system thus far known in literature is able to selectively catalyze the O-allylation of a phenol with allyl alcohol (or diallyl ether). Although allyl alcohol as allylating agent is reported in several cases in allylation reactions, the use of diallyl ether as allylating agent has only be mentioned once.[1] For selective O-allylation of phenols, it has often been reported that phenolate-salts are formed *in situ* in stoichiometric amounts by adding an excess of base to the reaction.[2,3] In the absence of such additives, allylation of phenols is observed; however, the thermodynamically favored C-allylated products are produced.[4,5]

The results obtained from the many experiments were eventually translated into a selective formation of the bisallyl ether of BPA. Patent applications have been reported about catalytic allylations of BPA, but with allyl acetate as the allylating agent.[6,7] In this prior art, selective

O-allylation has been reported, but again a base is needed to induce selectivity. In the absence of such a base, some diallyl ether of BPA is formed, but the selectivity is not properly documented and it has been reported in Chapter 9 that with the used catalytic system a high amount of trisallylated (and thus inevitably C-allylated) products are formed. A difficult issue of the bisallylation of BPA remains that it concerns a double equilibrium reaction. For the reaction of a phenol with any allylating agent, all catalysts reported in this thesis will eventually produce some undesired C-allylated product, when left for a long time to react. The observation that the desired O-allylated product is formed in a reversible reaction, while the C-allylated product is formed irreversibly, limits the yield of allyl phenyl ethers in a batch reaction. It is of key importance that the reaction is halted before C-allylated product form. In an industrial process, excess of allylation agent will be required to drive conversion to completion and recycling of this substrate will be clearly needed. The equilibrium of allyl phenyl ether formation is highly influenced by the amount of water present in the reaction mixture. For a large scale process, it would be beneficial to continuously extract the reaction water from the reactor to drive the allylation equilibrium to the product side. The use of a reaction solvent that results in very poor water solubility under reaction conditions, such as toluene or even parafin, provides an interesting possibility of a continuous reactive extraction of water by phase separating and removing the water phase continuously. The use of diallyl ether, directly derived from a condensation reaction of two molecules of allyl alcohol, as a new allylating agent, has also been a important discovery, since its use in allylation reaction intrinsically reduces the formation of water in the reaction significantly, thus allowing higher conversions in batch reactors. Although diallyl ether is not a chemical produced on large scale and therefore relatively expensive at this time, it can be easily produced by means of homo-allylation catalytic reaction of allyl alcohol with identical catalysts as used in the final allyl phenyl ether formation. The diallyl ether formed in a pre-reactor can thus be directly used in subsequent allylation reaction.

For both diallyl ether and allyl phenyl ether formation it would be very interesting to study the *in situ* extraction of the products from the reaction mixture, while leaving the remaining substrates to react further in the presence of the catalyst. This would circumvent the need for heterogeneous catalytic systems, since the catalyst can react in a homogenous reaction, which was shown in chapter 4 and 9 to be highly reactive, selective and stable (TONs of 200,000 are reported). The stability of allylation catalysts described in literature is often ignored and generally high catalyst loadings are used to induce a fast reaction. Heterogenization of the catalysts described in this thesis is possible, as was shown in Chapter 6, but the efficiency of

the catalyst decreases significantly. Considerably progress in heterogenization needs to be made to use such a catalyst in an industrial process. The scope on supports needs to be explored in combination with a stable linkage between catalyst and support. The removal of the catalyst with such supports after the reaction is also an interesting possibility for catalyst-recycling and should be studies in more depth.

Apart from ruthenium-based catalysts, also several palladium diphosphine complexes proved to be highly selective for O-allylation of phenols, maybe even more selective than their ruthenium analogues. The stability of this type of catalyst is considerably lower and the maximum turnover number is about a hundred times lower than that of best performing Ru-catalyst. The lower stability also masks the selectivity for O-allylation of phenols, since most of the catalyst is deactivated when the equilibrium for allyl phenyl ether is reached, therefore also preventing subsequent C-allylation. The relatively low stability of these Pd-catalysts is caused by the zero-valent oxidation state of the activated complex, leading to plating of inactive metallic Pd(0). During the catalytic cycle, the $L_2Pd(0)$ to $L_2Pd(II)$ transition is very sensitive, since it competes with the autocatalytic $Pd(0)_n + L_2Pd(0) \rightarrow$ cluster $Pd(0)_n$. Studies towards increased stabilization of such Pd(0) species are needed to obtain a catalyst applicable in an industrial process.

In the catalytic cycle of the Ru-catalyzed allylation reaction a $Ru(II) \rightarrow Ru(IV)$ transition is present, thus maintaining an ionic species throughout the cycle and therefore being much more stable.

Even though an industrial applicable process for the catalytic O-allylation of bisphenol A has not be developed thus far, the research discussed in this thesis can give important indications on how to proceed towards such a process. Nonetheless, the second step in the proposed route, epoxidation of the bisallyl ether of BPA, also needs to be highly efficient to finally form the bisglycidyl ether of BPA. Allyl phenyl ethers are cumbersome substrates in such epoxidation reactions, due to their low reactivity and poisoning of the catalyst via phenol formation.[8] In order to convert this system to an industrial applicable process, much more work needs to be done.

10.3 references

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Samenvatting

Algemene inleiding

De huidige productie van epoxyharscomponenten maakt gebruik van chloride-bevattende reagentia en levert grote hoeveelheden vervuilende gechloreerde bijproducten en zoutafval op. Voor de ontwikkeling van een chloorvrije route naar epoxyharsen is O-allylering van fenol gewenst, in het bijzonder van bisfenol A. De meeste allyleringsreacties maken gebruik van allyldonoren met goede vertrekkende groepen, zoals halides of acetaten. Deze reacties produceren nog steeds zoutafval en daarom is, vanuit een milieukundig oogpunt, allylalcohol het gewenste allyleringsagens aangezien hiermee alleen water wordt geproduceerd als bijproduct. Een groot nadeel van het gebruik van allylalcohol is de lage reactiviteit in allyleringsreacties vergeleken met allylhalides or acetaten. Allyleringsreacties van fenolen zijn beschreven in literatuur, echter, tot dusver moet een stoichiometrische hoeveelheid base toegevoegd worden om selectieve O-allylering te bereiken en C-allylering te voorkomen.
In Hoofdstuk 1 worden verscheidende types allyleringsreacties besproken en vergeleken, zowel voor allyldonoren met goede vertrekkende groepen als ook voor allylalcohol. Er wordt nadruk gelegd op $[RuCp(PP)]^+$-katalysatoren en de eigenschappen van fosfineliganden worden uitvoerig besproken.

$[RuCp(PP)]^+$ complexen in allylering van fenolen met allylalcohol als allyleringsagens

Een nieuwe katalytische methode is onderzocht om ofwel O- of C-geallyleerde producten van fenol te verkrijgen, gebruikmakend van allylalcohol of diallylether als allyldonor zonder toevoeging van stoichiometrische hoeveelheden additieven. Met behulp van de $[RuCp(PP)]^+$-katalysatoren beschreven in Hoofdstuk 2 kunnen beide reacties uitgevoerd worden met hoge selectiviteit. Er is aangetoond dat de O-geallyleerde producten reversibel worden gevormd, terwijl de C-geallyleerde producten irreversibel gevormd worden. Om deze reden is de selectiviteit van de reactie tijdsafhankelijk. Het blijkt dat een Ru-gekatalyseerde conversie van O-geallyleerde producten naar de thermodynamisch gunstige C-geallyleerde producten plaatsvindt onder reactiecondities. De structuur van het bidentaat ligand heeft echter een grote invloed op de katalytische activiteit en de chemoselectiviteit van de rutheniumkatalysator. Bovendien wordt een sterk co-katalytisch effect onthuld van toevoeging van kleine hoeveelheden zuur. Er wordt voorgesteld dat protonen de activeringsbarrières sterk verlagen

van zowel oxidatieve additie als reductieve eliminatie op het RuCp(PP)-centrum voor het substraat allylalcohol en de allylether producten. Beperkte coördinatieruimte op het rutheniumcentrum is gunstig voor de vorming van het O-geallyleerde product, terwijl toereikende ruimte door een zwak chelaat en/of een kleine coördinatiehoek gunstig is voor C-allylering. Het effect van chelaatstabiliteit op de selectiviteit van de reactie wordt nader onderzocht en besproken in het volgende hoofdstuk.

Een gem-dialkyleffect induceert hoge selectiviteit voor O-allylering van fenolen met allylalcohol

Katalysatoren met bidentaat fosfineliganden met geminale dialkylsubstituenten op het centrale atoom van de C_3-bruggende groep zijn erg selectief voor O-allylering, zoals beschreven is in Hoofdstuk 3. De thermodynamisch gunstige C-allylering kan zelfs gedurende lange reactietijden effectief geblokkeerd worden. Het blijkt dat de elektronische en structurele eigenschappen van de Ru(II)-complexen in de vaste fase niet significant verschillen van de complexen met ongesubstituteerde analoge liganden, terwijl de katalytische prestatie enorm verschilt. Dit resultaat suggereert dat de geminale dialkylsubstitutie op het centrale koolstofatoom van de C_3-brug van het ligand voornamelijk leidt tot een toename van de kinetische stabiliteit van het bidentaat chelaat onder reactiecondities. De oorzaak van het kinetisch-stabiele chelaat van deze liganden is een gereduceerde rotatievrijheid van de liganden. Daarom is de entropietoename bij dissociatie laag, hetgeen veroorzaakt dat het ligand gecoördineerd blijft op ruthenium, daarbij hoge selectiviteit voor O-allylering inducerend. Verwacht wordt dat de starheid van het ligand ook de oxidatieve additie hindert van allyldonoren op Ru(II), hetgeen wordt gezien als de snelheidsbepalende stap. Dit verklaart de relatief lagere activiteit van complexen met geminaal gesubstitueerde C_3-gebrugde liganden. De resultaten leveren een interessant voorbeeld van toepassing van de geminale dialkylsubstitutie op de brug van een bidentaat ligand als een diagnostische middel voor detectie van de selectiviteitbepalende stap in een katalytisch cyclus in homogene katalyse.

Katalysator actief voor of isomerisatie of allylering van allyl alcohol

In Hoofdstuk 4 wordt gerapporteerd dat de zeer actieve allylalcohol redox–isomerisatiekatalysator $[RuCp(PPh_3)_2](OTs)$ door toevoeging van een katalytische hoeveelheid sterk zuur zijn katalytische activiteit verandert naar de O-allylering van fenol met

allylalcohol. Hoge omzettingen (75.000 gebaseerd op fenol, 200.000 gebaseerd op allylalcohol) worden behaald en de katalysator is erg stabiel in aanwezigheid van substraat. Deze stabiliteit neemt af met de afnemende concentratie van substraat bij hoge conversie. Toevoeging van trifenylfosfine aan het reactiemengsel leidt niet tot verdere stabilisatie van de katalysator, maar tot de snelle allylering van het vrije fosfine en vorming van allylfosfoniumzouten. In deze reactie wordt het zuur geconsumeerd, hetgeen het katalytisch systeem deactiveert voor allyleringsreacties. Gecoördineerd trifenylfosfine wordt echter niet geallyleerd, wat wijst voor de allylering van fosfine op een aanval van trifenylfosfine van buitenaf het complex. De katalysator met monodentaat liganden is superieur in zowel activiteit als selectiviteit in vergelijking met katalysatoren met bidentaat fosfineliganden. Behalve fenol kan ook thiofenol efficiënt geallyleerd worden. Een meer uitgebreid onderzoek naar het toepassingsgebied van de allyleringskatalyse wordt besproken in het volgende hoofdstuk.

Verkenning van het toepassingsgebied van de allyleringsreactie gekatalyseerd door [RuCp(PP)]$^+$-complexen

In Hoofdstuk 5 wordt het toepassingsgebied verkend van de allyleringsreactie besproken in de voorgaande hoofdstukken. Er wordt aangetoond dat behalve fenolen ook primaire, secundaire en zelfs tertiaire alcoholen succesvol geallyleerd kunnen worden met allylalcohol of diallylether als allyleringsagens. Hierbij wordt hoge selectiviteit voor de alkylallylether verkregen. De reactiviteit van alifatische alcoholen is in de volgorde primair > secundair >> tertiair. Een thermodynamische voorkeur voor de vorming van een alkylallylether over diallylether is gevonden. Behalve alcoholen kunnen ook thiolen en indool efficiënt geallyleerd worden. Aniline werkt echter als een katalysatorremmer. Gesubstitueerde allylische alcoholen met een terminale olefinegroep vertonen een hogere reactiviteit dan allylische alcoholen met een interne olefinegroep. Voor deze laatste soort zijn cis-allylische alcoholen reactiever dan trans-allylische alcoholen. Het substitutiepatroon van gesubstitueerde allylische alcoholen blijft vrijwel onveranderd tijdens en na de reactie, wijzend op een relatief langzame σ-π allylisomerisatie op het Ru(IV) intermediair ten opzichte van reductieve eliminatie.

Immobilisatie van [RuCp(PP)]$^+$-complexen en de reactiviteit in allyleringsreacties

[RuCp(PP)]$^+$-complexen die actief zijn voor allylering van alcoholen met allylalcohol als allyleringagens zijn geïmmobiliseerd op vaste dragers, zoals beschreven in Hoofdstuk 6.

Twee verschillende methoden zijn gebruikt voor immobilisatie: (1) via elektrostatische interacties op ionenwisselaars, waarbij het anion aanwezig is op de drager en (2) via een coördinatiebinding, waarbij het fosfineligand covalent gebonden is op de drager. Beide methoden geven hoge opbrengst aan geïmmobiliseerd complex met relatief gemakkelijke procedures. De katalysatoren die geïmmobiliseerd zijn via ionogene interacties allyleren zowel 1-octanol als 4-*tert*-butylfenol met zeer lage uitwassing van de katalysator. Deze katalysator is in de allylering van fenol echter volledig selectief voor C-allylering. Vanwege de hydrofiele harsen die gebruikt zijn, wordt water ingevangen en dit is erg nadelig voor de O-allylering van fenol. De immobilisatie van rutheniumkatalysatoren door middel van coordinatiebinding op drager zonder hydrofiele residuen maakt O-allylering mogelijk. Alhoewel uitwassing van deze rutheniumverbinding uit de hars enigszins hoger is dan voor de katalysator geïmmobiliseerd op ionenwisselaars, is de activiteit over meerdere reacties relatief stabiel. Quarternisering van de overmaat fosfine aanwezig op de drager speelt een belangrijke rol voor de activiteit van de katalysatoren voor de allyleringsreactie. De activiteit van de heterogene systemen beschreven in dit hoofdstuk is aanzienlijk lager dan die van de analoge homogene katalysatoren.

Theoretische studie naar de Ru-gekatalyseerde allylering van fenol met allylalcohol

De twee stappen in het mechanisme van katalytische allyleringen met $[RuCp(PP)]^+$ complexen die activiteit en selectiviteit bepalen zijn respectievelijk een oxidatieve additie en een reductieve eliminatie. De intermediaire verbindingen, voorgesteld in de voorgaande hoofdstukken, die een sleutelrol spelen in deze stappen zijn gemodelleerd met Density Functional Theory, zoals beschreven is in Hoofdstuk 7. Berekeningen zijn gemaakt voor de situatie in zowel afwezigheid als aanwezigheid van zuur. De energetische effecten van het veranderen van de chelerende fosfine liganden worden waargenomen voor de oxidatieve additie en de reductieve eliminatie. Observaties gemaakt tijdens experimenten in voorgaande hoofdstukken worden zichtbaar in de berekeningen. Het gebruik van *gem*-diakyl gesubstitueerde fosfineliganden in de katalysatoren stabiliseert fosfinecoördinatie in de Ru(IV)-toestand. Het berekende effect is meer significant voor complexen met een C_1-bruggende groep dan voor een C_3-bruggende groep. Voor C_1-bruggende groepen heeft dit effect een elektronische origine, hetgeen in de berekeningen wordt weergegeven, terwijl voor C_3-bruggende groepen dit effect een entropische origine heeft, dat niet bepaald kan worden met de berekeningsmethode die is gebruikt.

Palladium complexen met bidentaat fosfineliganden als katalysator voor allylering met allylalcohol

Enkele palladiumcomplexen met bidentaat fosfineliganden zijn getest voor hun activiteit in the O-allylering van fenolen met allylalcohol. De katalysatoren beschreven in Hoofdstuk 8 hebben geen droogmiddel of een stoichiometrische hoeveelheid additieven nodig om activiteit te induceren. Complexen met een chelerend fosfineligand met een C_3-bruggende groep laten erg hoge selectiviteit voor O-allylering van fenolen zien. Het gebruik van *gem*-dialkyl substituenten verhoogt de conversie van de reactie, waarschijnlijk door een toename van de stabiliteit van het intermediaire Pd(0)-deeltje. Het gebruik van diallylether als allyleringsagens leidt tot een significante verhoging van de conversie zonder verlies van selectiviteit. Het gebruik van $Pd(II)(OAc)_2$ en $Pd(0)(dba)_2$ als pre-katalysator in combinatie met fosfineliganden resulteert in beide gevallen tot de vorming van actieve katalysatoren. Katalysatoren met fosfine liganden met niet-gesubstitueerde fenylringen geven een hogere activiteit dan katalysatoren met fosfineliganden met *ortho*-methoxy-gesubstituteerde fenylringen, waarschijnlijk door coördinatie van de methoxygroep. Met het gerapporteerde katalytische palladiumsysteem kunnen niet alleen fenol, maar ook alifatische alcoholen, aromatische en alifatische amines geallyleerd worden.

Bisfenol A als het ultieme substraat in selectieve O-allylering van fenolen

De O-allylering van bisfenol A (BPA) is uitgevoerd met de meest selectieve katalysatoren voor O-allylering van fenolen. Om een hoge selectiviteit voor O-allylering zonder stoichiometrische additieven, zoals basen, te behalen, is de katalysatorstructuur de bepalende factor. Zowel $[RuCp(PPh_3)_2](OTs)$ in de aanwezigheid van zuur als $Pd(OAc)_2$ met het fosfineligand dppdmp blijken, zoals beschreven in Hoofdstuk 9, erg selectief voor de O-allylering van BPA. Relatief hoge opbrengsten van de bisallylether van BPA worden behaald. De keuze van het oplosmiddel is cruciaal voor hoge conversie en selectiviteit. Het gebruik van een overmaat diallylether resulteert in goede opbrengsten voor de bisallylether van BPA, terwijl de selectiviteit voor O-allylering behouden blijft.

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Curriculum Vitae

Jimmy Antonius van Rijn werd op 21 november 1981 geboren te Voorburg. Na het behalen van het VWO-diploma aan het Veurs College te Leidschendam in 2000 werd in september van dat jaar begonnen met de studie Scheikunde aan de Universiteit Leiden. Van maart 2003 tot maart 2004 werd in het kader van de hoofdvakstage onderzoek verricht bij de vakgroep Bio-Organische Synthese onder leiding van Prof. Dr. H.S. Overkleeft. Dit onderzoek omvatte de synthese van identificatielabels en remmers voor proteases. Bovendien werd van november 2004 tot mei 2005 onderzoek verricht in de vakgroep van Prof Dr. P.S. Seeberger aan de Eidgenössische Technische Hochschule (ETH) in Zürich aan *De-Novo* synthese van glycoamines. Het doctoraaldiploma werd in november 2005 behaald.

Van december 2005 tot maart 2010 werd als Assistent in Opleiding in dienst van de Universiteit Leiden, het in dit proefschrift beschreven onderzoek uitgevoerd bij de vakgroep coördinatie en bio-anorganische chemie onder leiding van Prof Dr. E. Drent en Dr. E. Bouwman.

Tijdens de promotieperiode zijn de volgende cursussen gevolgd en afgerond: *Catalysis, an integrated approach* (NIOK), Communication in Science (Universiteit Leiden), Physical methods in inorganic chemistry (HRSMC) en Advanced Metal-Organic Chemistry (HRSMC). Delen van het in dit proefschrift beschreven werk werden gepresenteerd tijdens de nationale NCCC bijeenkomsten (NCCC VIII-X) te Noordwijkerhout 2007-2009, de International School of Organometallic Chemistry 2007 te Camerino, Italië, de International Conference on Organometallic Chemistry 2008 te Rennes, Frankrijk en de EuCheMS Conference on Organometallic Chemistry 2009 te Götenburg, Zweden.

In de zomer van 2010 zal als Process Researcher worden begonnen bij Hexion Specialty Chemicals in Pernis.