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

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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

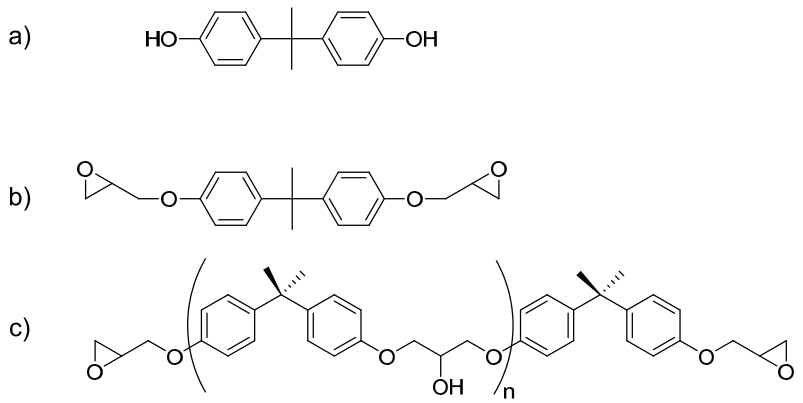
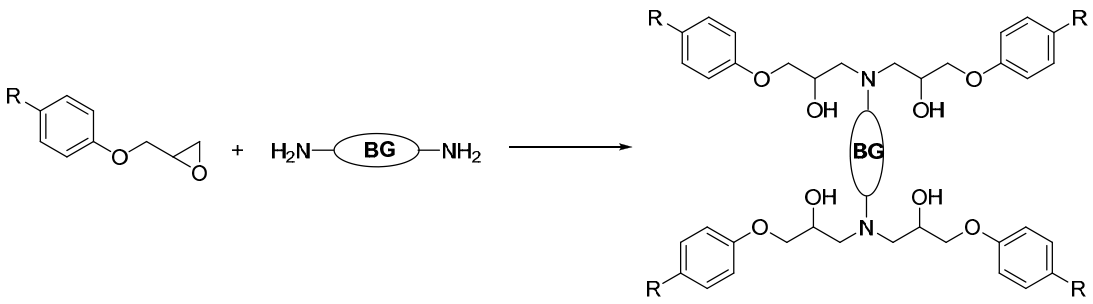


Figure 1.1. General structure of a) bisphenol A b) structure of diglycidyl ether of bisphenol A and c) general structure of diglycidyl ether of bisphenol A resin.



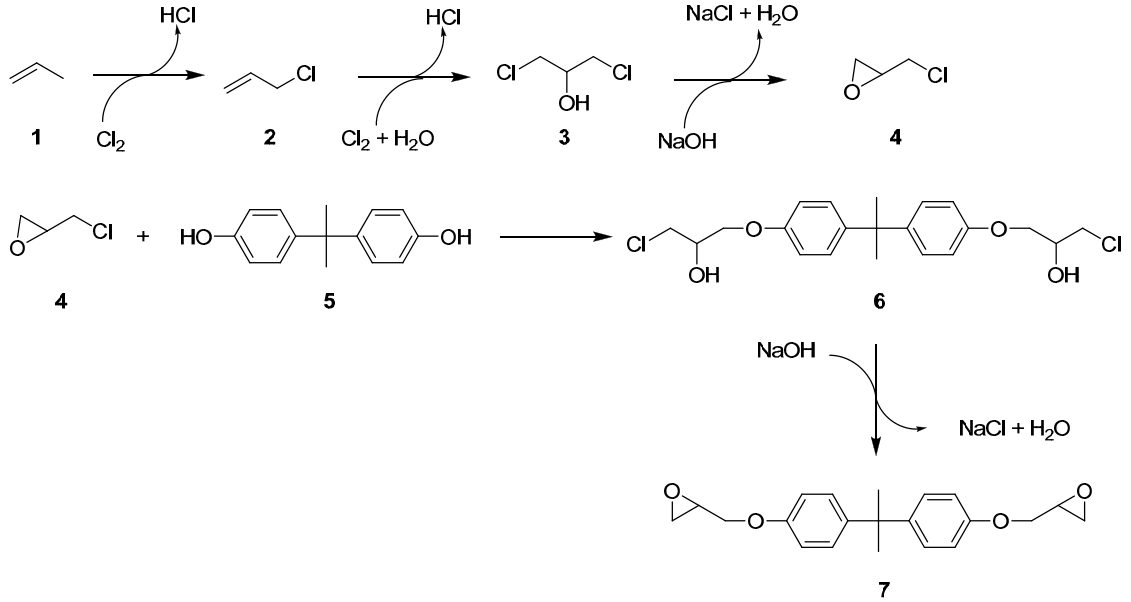
Scheme 1.1. Curing mechanism for epoxy resins (BG = bridging group).

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

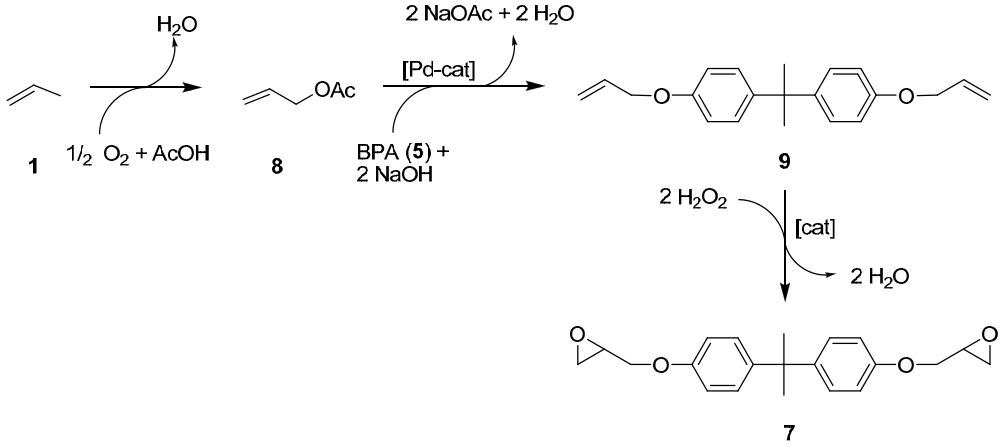


Scheme 1.2. Current process towards bisphenyl A diglycidyl ether.

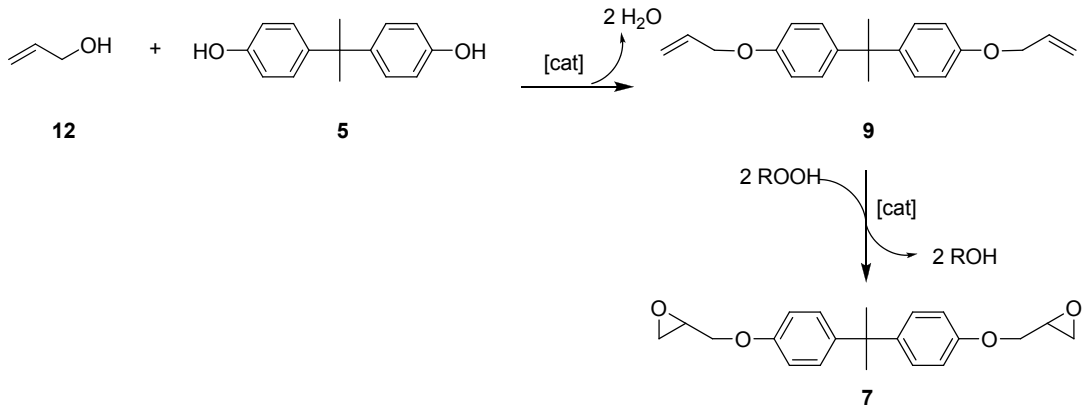
allyl chloride and epichlorohydrin, as well as in the formation of the final product. Large excess water is needed to minimize byproduct formation which makes the process energy intensive in order to separate ECH from the large water stream. A different process which is much less energy intensive and 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.

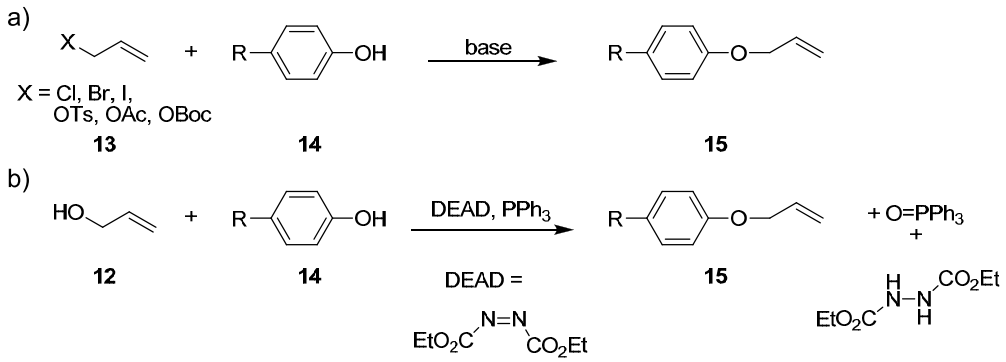


Scheme 1.4. Proposed chlorine-free and salt-free process towards bisphenyl A diglycidyl ether (**7**).

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

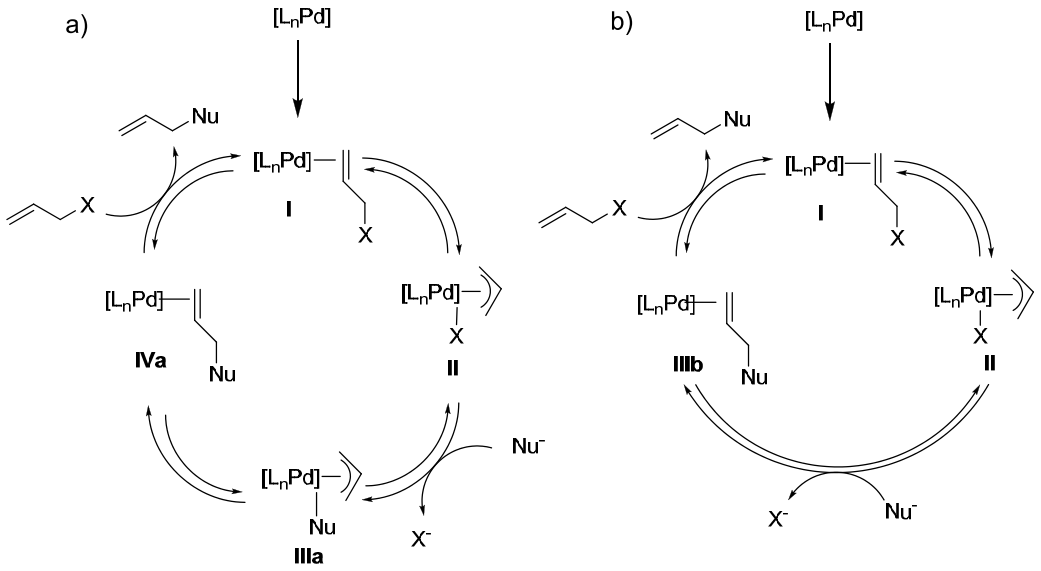
Classically, phenyl allyl ethers are obtained by the Williamson ether synthesis, in which allyl species with a good leaving group, such as halides, tosylates, carboxylates or carbonates (Scheme 1.5a), are reacted with a phenol under the agency of stoichiometric amounts of base.[13-16] Also Mitsunobu-type 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

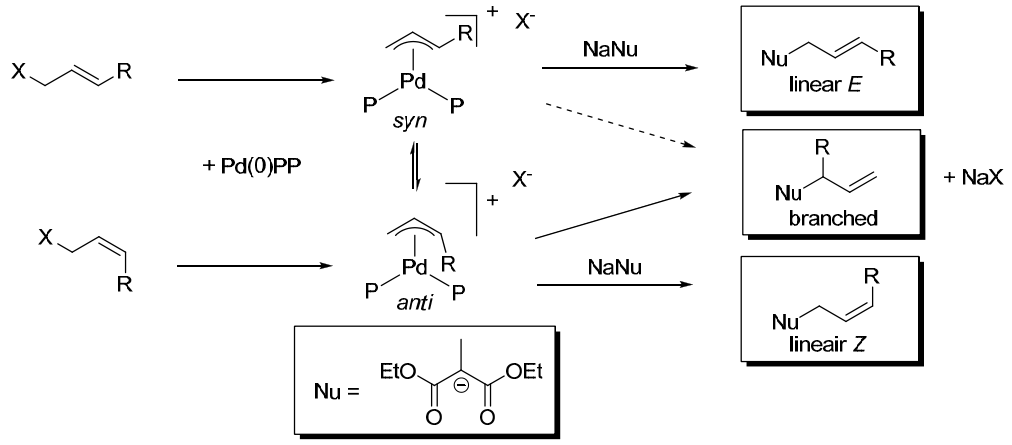
The allyl group is a highly used reactive group in organic chemistry and various types of catalytic allylation reaction have been reported. In most cases, allyl donor molecules are used with good leaving groups. A well-known allylation reaction is the palladium-catalyzed Tsuji-Trost allylic alkylation[22,23] 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)

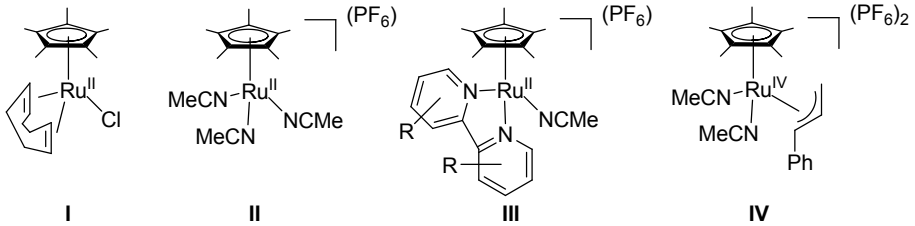
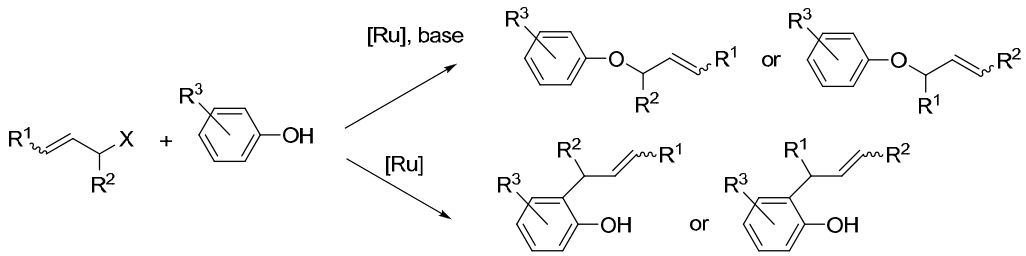


Figure 1.2. RuCp*- complexes used as catalysts for allylation reactions.

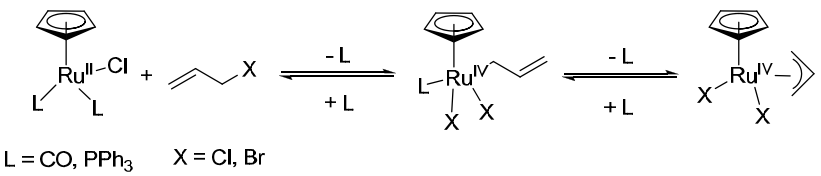


Scheme 1.8. O-and C-allylation of phenolic compounds in the presence of ruthenium catalysts.

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

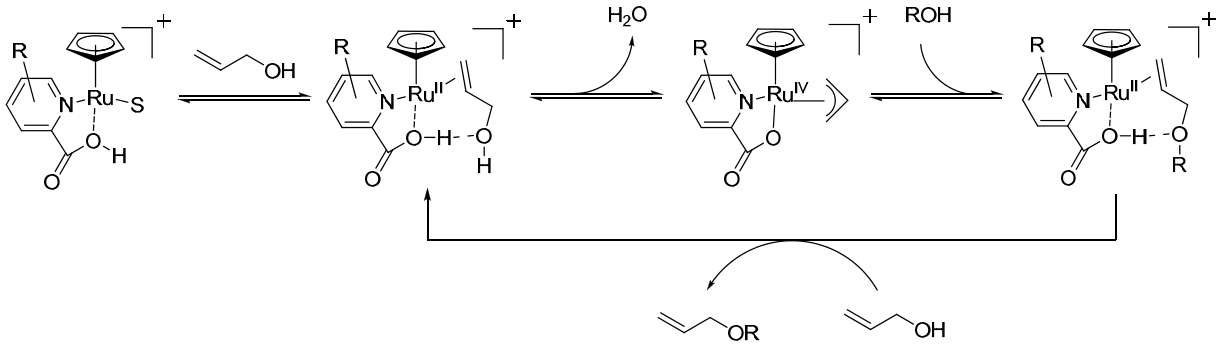
Apart from palladium- and ruthenium-based catalysts other transition metal complexes are known to catalyze allylation reactions. An iridium complex, $[Ir(cod)_2]BF_4$ has been reported to catalyze the reaction between aliphatic alcohols and allyl acetate to yield allyl alkyl ethers in quantitative yields.[57] 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.

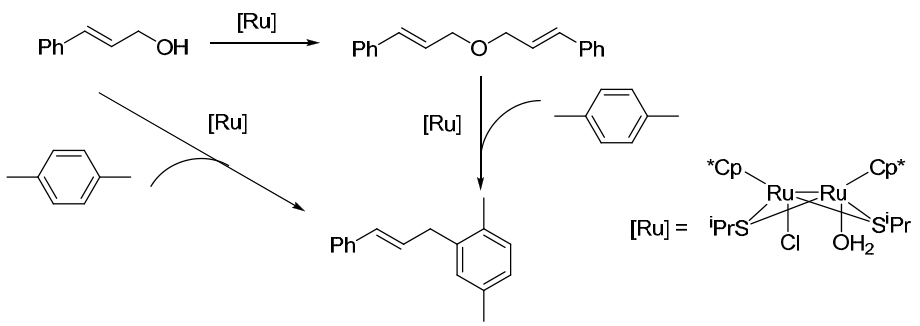
A Pd-triphenyl phosphite catalyst has been reported to show high activity for the allylation of aliphatic alcohols with various types of allyl alcohols.[62] Besides cross-allylations, also the reaction of allyl alcohol with itself is observed, forming diallyl ethers. Interestingly, no addition of stoichiometric 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]

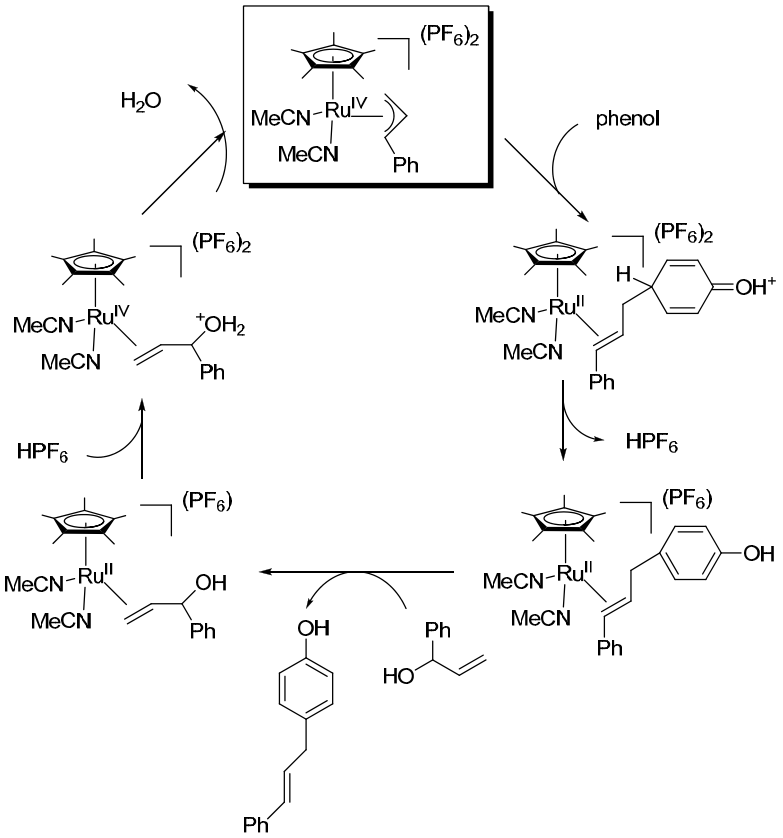
obtain a Ru(II) species coordinated to the allyl ether. After exchange of the product with a new molecule of allyl alcohol, the catalytic cycle is completed. Although all the elementary steps in the cycle are reversible, the phase separation of water from the reaction mixture and the low nucleophilicity 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]

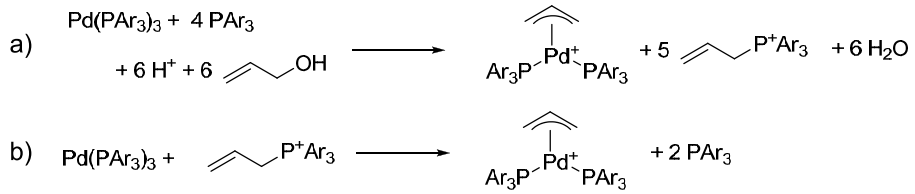
A ruthenium-based catalytic system has been reported to catalyze the allylation of phenols with allyl alcohol, but again, only C-allylated products are formed.[74] The catalyst precursor is a Ru(IV)Cp*(allyl) compound, which means that the catalytic cycle is entered after oxidative addition of the allyl 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]

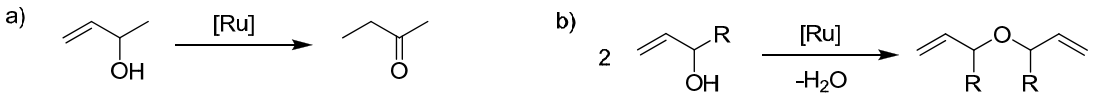
conditions without acid addition, hydroxide is formed and the pH of the medium slowly increases. Interestingly, only one of the initially coordinated phosphines reacts with allyl alcohol, but only because this phosphine is replaced by coordination of allyl alcohol onto the palladium catalyst and freely 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.

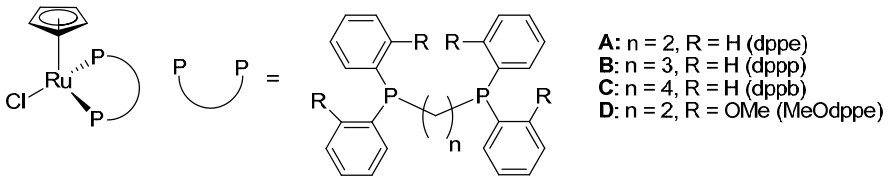
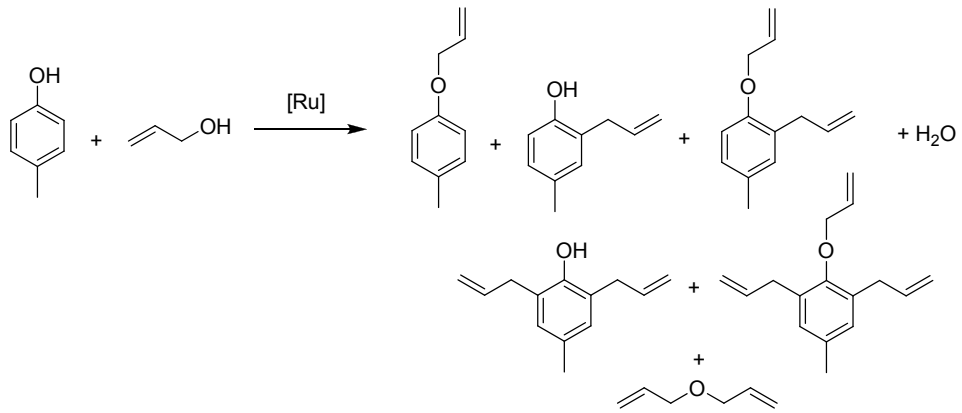


Figure 1.3. Structures of ruthenium complexes showing activity in the catalytic allyl ether formation.[82]

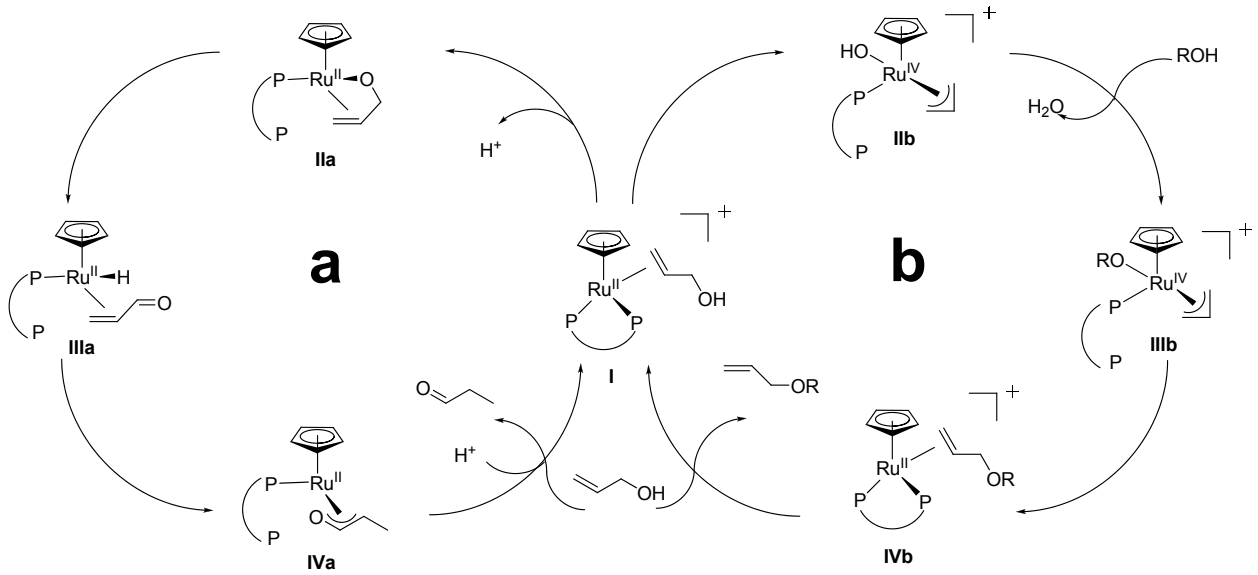
making it the first $[RuCp(PP)]^+$ complex that catalyzes O-allylation in the absence of stoichiometric amounts of base. The catalyst is also quite active and only low concentrations of catalyst are needed. However, the formed allyl phenyl ether undergoes further reactions, yielding a mixture of several 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.

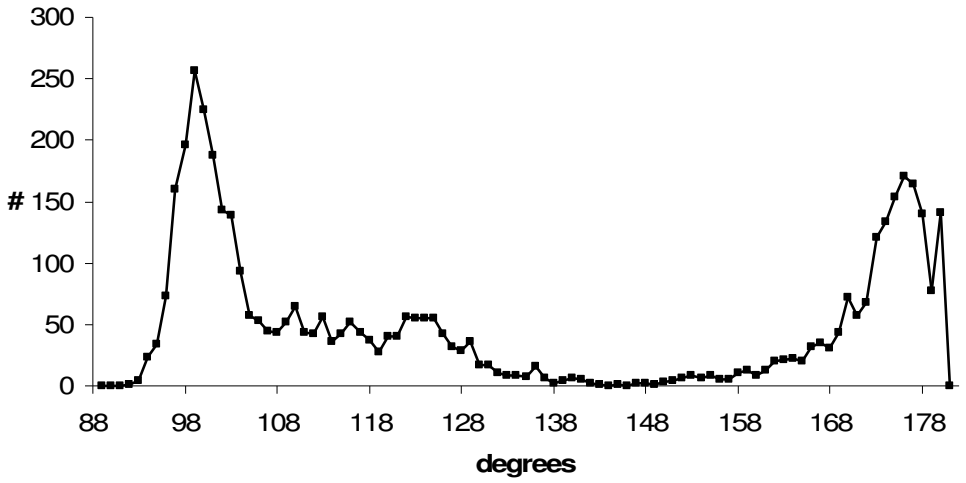


Figure 1.4. Number of (PP)M fragments (#) with P = PPh_3 found in a CSD search**.**

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

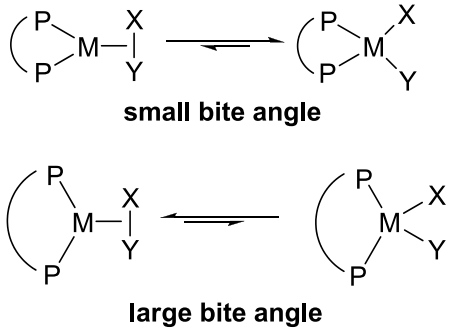


Figure 1.5. a) steric influence of P-M-P angle on reaction space α and b) influence of reaction space on oxidative addition and reductive elimination.

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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