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

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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) → 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.

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