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

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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

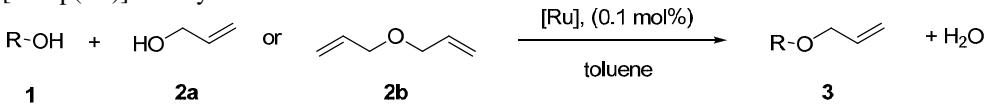
The use of $[RuCp(PP)]^+$ complexes in the catalytic allylation of phenols with allyl alcohol has been demonstrated (Chapter 2-4). It was observed that during this process, allyl alcohol also reacts with itself as the nucleophilic alcohol to form diallyl ether. It is therefore interesting to broaden 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]



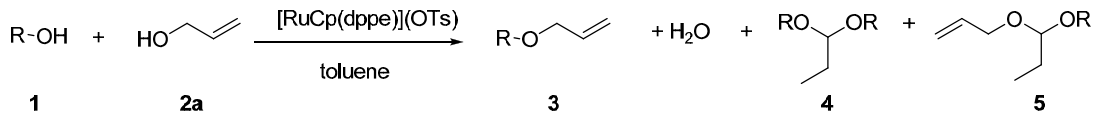
entry	R =	allyl donor	yield of **3** (%)
1[b]	1-octyl	2a	52
2	1-octyl	2a	100
3	1-butyl	2a	100
4	Ethyl	2a	86
5[c]	1-octyl	2b	84
6[c]	1-butyl	2b	88
7[c]	Ethyl	2b	97
8[c]	1-octyl	allyl butyl ether	42

[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.

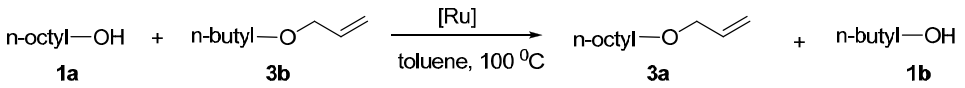
5.2 Results and discussion

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**.

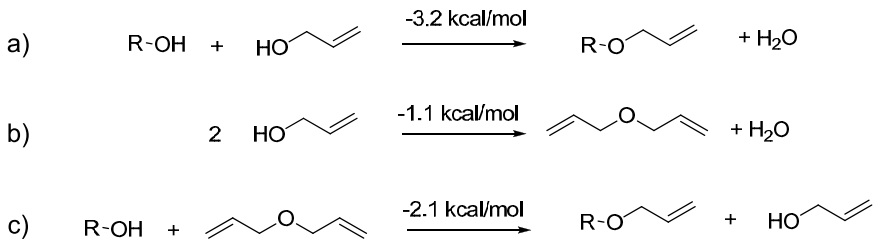


Scheme 5.2. Transallylation between 1-octanol and allyl butyl ether.

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]

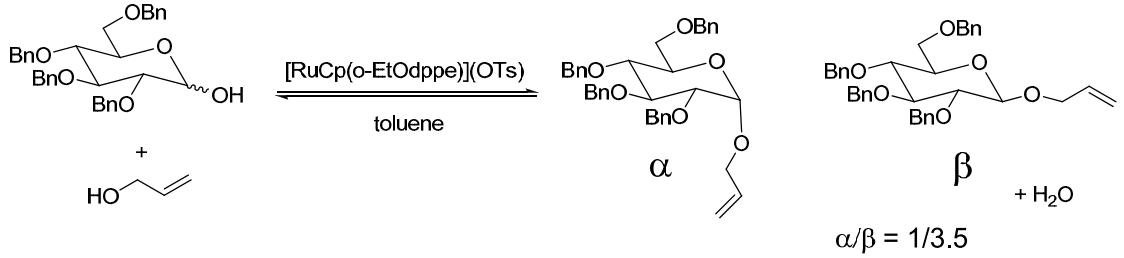
entry	alcohol	rate constant k (h^{-1})[b]	yield of **3** (%)
1	1-octanol	4.61	100
2	cyclohexanol	1.43	75
3	2-adamantanol	1.12	82
4	1-adamantanol	0.02	10
5[c]	1-adamantanol	0.78	52
6	2,3,4,6-tetra-O-benzyl-D-glucose	-	80[d]
7[e]	4-*tert*-butylphenol	1.02	68

[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



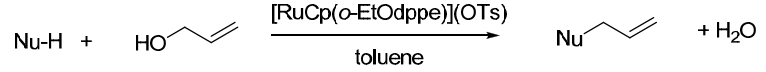
Scheme 5.4 Ru-catalyzed allylation of 2,3,4,6-tetra-O-benzyl-D-glucose with alcohol and it selectivity.

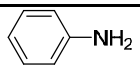
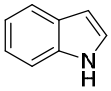
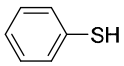
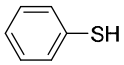
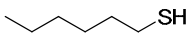
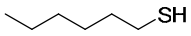
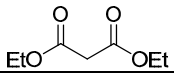
hydroxyl groups except for the anomeric position. The reaction shows a high conversion towards the allyl ether. An α to β ratio of 1/ 3.5 (Scheme 5.4) was found as was deduced from the ^{1}H-NMR spectra.[18,19] The preference for the sterically less hindered β-product is most likely induced by the relative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



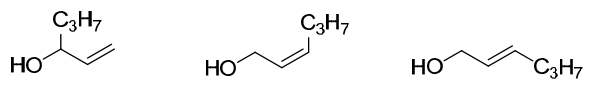
entry	Nu-H	reaction time (h)	conversion of NuH (%)
1		2	0
2		2	85
3		2	38
4		20	48
5		2	12
6		20	78
7		2	0

[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

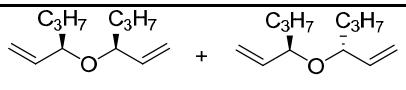
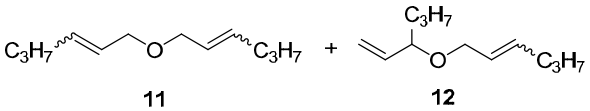
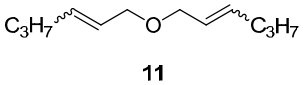
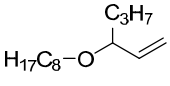
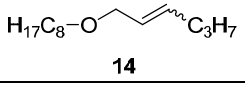
Apart from broadening the scope on the nucleophilic substrates, also substituted allylic alcohols were investigated on their reactivity in the ruthenium-catalyzed system. Different substitution patterns were explored and both branched as well as linear, cis and trans allylic alcohols were used (Figure 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]

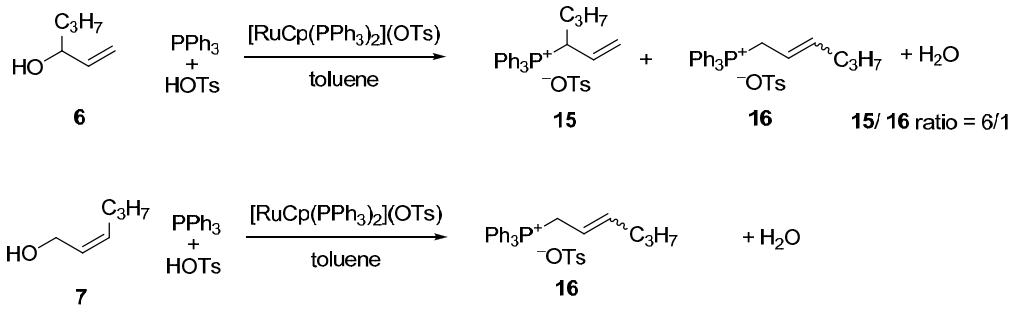
entry	substrate	conversion of **6**-**8** (%)	products formed	selectivity to products (%)
1	**6**	51	 **9** + **10**	50 (**9**) 50 (**10**)
2	**7**	29	 **11** + **12**	75 (**11**) 25 (**12**)
3	**8**	3	 **11**	100 (**11**)
4	**6** + 1-octanol	81	 **13**	100 (**13**)
5	**7** + 1-octanol	31	 **14**	100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

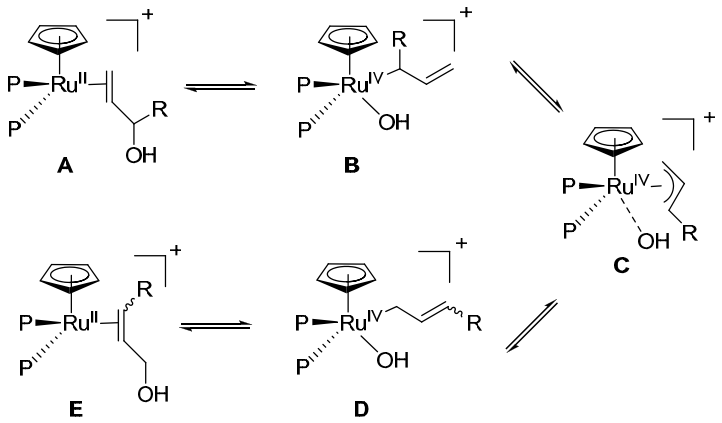
Thiols are demonstrated to react with complete selectivity for the S-allylated product. The higher nucleophilicity of thiophenolate as compared to phenolate most likely promotes formation of allyl sulfides, but also the increase in size of the nucleophilic donor atom may cause the high selectivity, as 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.

5.5 References

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