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First direct α -allylation of carbonyl compounds using ruthenium catalysts

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Abstract: Direct α -allylation of aldehydes and ketones have been carried out with allyl alcohol or diallylether in the presence of the ruthenium catalyst RuCp(PPh₃)₂OTs. The presence of PTSA appeared necessary to prevent isomerization of allyl alcohol into propanal. A large variety of aldehydes and ketones could be allylated in those conditions with high yields.

Keywords: allylation; carbonyl compounds, ruthenium; catalysis.

1. Introduction

Carbonyl compounds are valuable molecules which are found in numerous pharmaceuticals, cosmetics and perfumes as natural or synthetic molecules. The development of clean and efficient processes to produce new structures based on the transformation of the carbonylated skeleton is of interest due to the large panel of possible applications. Particularly attractive is C-C bonds formation in ketones or aldehydes without altering the carbonyl group. The synthesis of α -allylated carbonyl compounds is particularly attractive to open the way to further diversifications. The C=C double bond can be efficiently converted and further functionalized thanks to, for example, oxidation, hydroformylation or metathesis reactions. Synthesis of α -allyl carbonyl products could be performed from Claisen rearrangement of allyl vinyl ethers according to a multistep protocol [1,2]. On the other hand, metal-catalyzed allylic alkylation is a reliable and more straightforward method for C-C bonds formation. Initially reserved for stabilized carbanions such as malonates, α -allylation has been developed on aldehydes and ketones via their corresponding enolates [3-6], enol silyl ethers [7,8] or enamines [9]. Various activated allyl electrophiles as allyl halides, carbonates or acetates have been used with the major drawback to generate great quantities of co-products. Nevertheless, these reactions could also be carried out with allylic alcohol thanks to a judicious choice of the catalytic system [10,11]. In concordance with concepts of green chemistry, the use of allyl alcohol is much more advantageous with the formation of water as sole by-

product. The most frequently used transition metal in the allylic alkylation is palladium [12], but rhodium [13], iridium [14], platinum [15] or ruthenium [16, 17] are also suitable. Recent developments have revealed the potential of first row transition metals (Cu, Co and Ni) in allylic alkylation [18]. Our team previously developed an efficient and sustainable nickel-catalyzed α -allylation of carbonyl compounds with allyl alcohol [19-21]. The reaction was performed under neutral conditions without addition of any additive or base. The experimental conditions allowed the efficient conversion of α -branched aldehydes and ketones. However, in the case of linear aldehydes, self-aldol condensation occurs before allylation reaction. Furthermore, Ni(cod)₂-based catalytic precursors are relatively unstable in air, reducing their industrial attractiveness. With these results in mind, we turned our attention towards ruthenium catalysts which proved to be efficient in allylation reaction with allyl alcohol [22,23]. To our knowledge, no publication reports the direct α -allylation of aldehydes and ketones in the presence of ruthenium catalysts. One limitation with the use of ruthenium relies in its propensity to catalyze the isomerization of allyl alcohol in propanal. Interestingly, it has been shown that the presence of an acid prevents this reaction and this has been used to optimize the allylation of phenols (ether synthesis) with allyl alcohol promoted by [RuCp(PPh₃)₂](OTs) at relatively mild temperature. This catalytic precursor proved to be also effective in the allylation of various nucleophiles such as aliphatic alcohols, thiols and amines [24]. This prompted us to evaluate the α -allylation of aldehydes and ketones with [RuCp(PPh₃)₂]X as precursor (Figure 1).

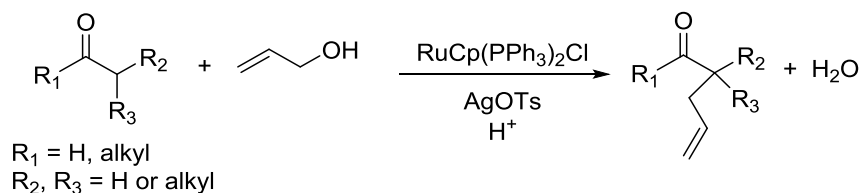


Figure 1. The α -allylation reaction of carbonyl compounds with allyl alcohol/ether.

2. Experimental

2.1. General information

Chemicals were purchased from Aldrich, TCI (reagents and solvents) and Strem (ruthenium precursor and ligands). Common solvents were distilled and degassed before use. The reactions were performed under nitrogen atmosphere using standard Schlenk line techniques. NMR spectra were recorded using a Bruker AC 300 spectrometer. ¹H and ¹³C NMR chemical shifts are reported to the solvent resonance [CDCl₃: 7.27 ppm (¹H), 77.0 ppm (¹³C)].

2.2. Synthesis of the complex $\text{RuCpCl}(\text{PPh}_3)_2$ [25]

The ruthenium complex was synthesized according to a literature procedure [25]. 5 g (0.024 mole) of $\text{RuCl}_3 \cdot x \text{H}_2\text{O}$ were dissolved in 100 mL absolute ethanol at 60 °C. 10 mL (0.121 mole) of fresh distilled cyclopentadiene were then added. This solution was transferred drop by drop for 10 min in a 2 L flask in which 21 g (0.080 mol) of PPh_3 in 1.2 L of ethanol were prior introduced. The mixture was heated at reflux for 1.5 h. The solution was hot-filtered and the precipitate was dried under vacuum.

Yield : 80 %, orange solid.

2.3 Synthesis of the complexes $\text{RuCpCl}(\text{diphosphine})$ [23,26]

$\text{RuCpCl}(\text{PPh}_3)_2$ (101 mg, 0.14 mmol) and the diphosphine (dppb, dppe or dppf : 1.2 equiv.) in toluene (5 mL) were heated 16 h at 90 °C. Complexes were purified on alumina column chromatography.

Yields: $\text{RuCpCl}(\text{dppb})$: 75 %; $\text{RuCpCl}(\text{dppe})$: 70 % $\text{RuCpCl}(\text{dppf})$: 91 %.

2.4. General procedure for allylation of carbonyl compounds

The catalyst $\text{RuCpCl}(\text{PPh}_3)_2$ (1 mol%), PTSA (26 mol%), AgOTs (3.6 mol%) were weighted in a Schlenk tube. In a second Schlenk tube, allyl alcohol (4 mmol) or diallylether (2 mmol) and the carbonyl substrate (2 mmol) were dissolved in the solvent (0.5 mL THF or toluene). The solution was degassed using the freeze pump thaw method and transferred under nitrogen in the tube with the solids. The reaction mixture was stirred at 60 °C for 3 or 17 h.

2.5. Analyses and characterizations of the products

For determination of carbonyl compounds conversion, the crude was homogenized with 0.5 mL methanol if necessary and a precise quantity of dodecane (1 mmol) was added as internal standard. Conversions were determined by gas chromatography on Shimadzu 2010 equipped with a column HT-5 (30 m, i.d. = 0.32 mm). The products were purified by silica gel column chromatography using petroleum ether/ CH_2Cl_2 as eluent for aldehydes and petroleum ether/ethylacetate as eluent for ketones.

The NMR spectra of the new products can be found in the supporting information.

3. Results and discussion

Our work was first focused on the α -branched aldehydes allylation. In order to determine the optimal reaction parameters, the study was performed on the ruthenium catalyzed allylation of cyclohexane carboxaldehyde **1a** as model substrate (Figure 2). Experimental conditions were similar to those used during phenol allylation with $\text{RuCpCl}(\text{PPh}_3)_2$ as catalytic precursor [22]. AgOTs was added to the reaction mixture to displace chloride anion with tosylate group through formation of AgCl. *p*-Toluenesulfonic acid (PTSA) was also added to the reaction medium to promote the allylation reaction and limit the isomerization of allyl alcohol to propanal. In a classical procedure, the ruthenium precursor, PTSA (52 %) and silver tosylate were weighted under nitrogen. Allyl alcohol **2a** solubilized in the chosen solvent was then added to the solids and the mixture was heated for 17 h at the desired temperature. All details of the experiments are described in the experimental part. Results are reported in Table 1.

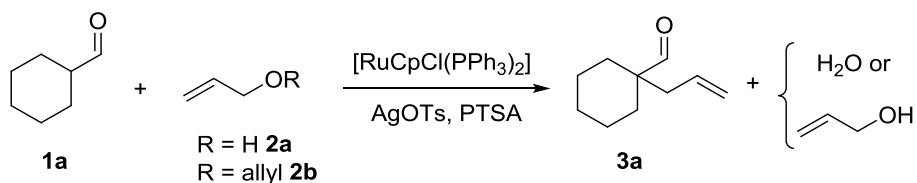


Figure 2. The α -allylation reaction of cyclohexane carboxaldehyde **1a**.

Table 1. Ruthenium catalyzed α -allylation of cyclohexane carboxaldehyde **1a**.^{a)}

Entry	Allyl compound	Equiv. allyl compound	T (°C)	Solvent	Yield 3a (%) ^{b)}
1	Allyl alcohol 2a	2	60	Toluene	40
2		3	60	Toluene	70
3		5	60	Toluene	74
4		3	80	Toluene	60
5 ^{c)}		3	60	Toluene	25
6	Diallylether 2b	2	60	Toluene	98
7		2	60	MeOH	35
8		2	60	EtOH	50
9		2	60	DMSO	0
10		2	60	Neat	27
11		2	60	THF	96
12		1	60	THF	66
13		0.5	60	THF	45

a) Cyclohexane carboxaldehyde **1a** (2 mmol), [RuCpCl(PPh₃)₂] (1 mol%), PTSA (52 mol%), AgOTs (3.6 mol%), solvent : 0.5 mL, 17 h. b) Determined by GC analysis using dodecane as internal standard. c) 2 eq H₂O vs aldehyde.

The first ruthenium catalyzed allylation was performed in toluene at 60 °C with 2 equivalents of allyl alcohol **2a**. Product **3a** was isolated after column chromatography, demonstrating the potential for α -allylation of aldehydes using ruthenium catalysis. However, under these conditions, a low yield of 40 % was obtained (entry 1). The number of equivalent of allyl alcohol was increased up to 5. With 3 equivalents, a significant increase of the yield to 70 % was observed (entry 2). The use of 5 equivalents had no impact on the yield of the reaction, which reached a plateau at 74 %. Temperature was also increased to 80 °C but in that case, a lower reactivity was observed (entry 4) probably due to a degradation of the catalyst at that temperature. It was observed that the color of the catalyst in solution changed progressively during the reaction, from light yellow to dark orange. One possible explanation is the impact of water generation on catalysis. To assess this hypothesis, a reaction was carried out with 2 equivalents of water initially added to

the reaction (entry 5). The reaction yield decreased substantially to 25 % in the presence of water, confirming the harmful effect of water on the reaction. To prevent this effect, an allylating agent that does not release water is best used. Interestingly, Bouwman had noted that dehydrative condensation of allyl alcohol to give diallylether tends to precede the allylation reaction of phenol [22]. We then evaluated diallylether **2b** which proved to be a good allylation reactant during ketones allylation with nickel catalysts [19–21]. We were pleased to observe that in toluene at 60 °C in the presence of 2 eq. of diallylether **2b**, 98 % of allylcyclohexane carboxaldehyde **3a** could be obtained (entry 6). The use of more polar solvents such as MeOH (entry 7), EtOH (entry 8) or DMSO (entry 9), that proved to be particularly interesting in nickel allylations, was not beneficial in the case of ruthenium. The solvent-free reaction gave a yield of 27 % (entry 10), but in that latter case, the catalyst was not well solubilized at the beginning of the reaction, favoring isomerization of allyl alcohol to propanal. The use of THF showed much greater efficiency in the allylation reaction, with a yield of 96 %, similar to that obtained with toluene (compare entries 6 and 11). A decrease of the diallylether **2b** quantity from 2 to 1 and finally 0.5 equivalent reduced the yield to 66 % and 45 % respectively (entries 12 and 13). Diallylether **2b** proved to be the allylation agent of choice for this application and was subsequently used for further allylation reactions.

Then the optimization was directed towards the acid. Various quantities of PTSA and different acids were evaluated (Table 2). The reaction mixture was analyzed after 3 h in order to compare the yields in the different conditions.

Table 2. Acid effect in the Ru-catalyzed allylation of cyclohexane carboxaldehyde **1a**.^{a)}

Entry	Acid	% acid	Yield 3a (%) ^{b)}
1	PTSA	52	71
2	PTSA	26	90
3	PTSA	6	95
4 ^{c)}	PTSA	0	51
5	MeSO ₃ H	26	<1
6	Amberlite	26	<1

a) Cyclohexane carboxaldehyde **1a** (2 mmol), diallylether **2b** (4 mmol), [RuCpCl(PPh₃)₂] (1 mol%), AgOTs (3.6 mol%), toluene : 0.5 mL, 60 °C, 3 h.

b) Determined by GC analysis using dodecane as internal standard.

c) t = 17 h.

In a reaction mixture with 52 % PTSA, the allylated carboxaldehyde cyclohexane **3a** was selectively produced (71 % yield, entry 1). Decreasing the acid percentage to 26 % resulted in a higher yield into the desired **3a** product (90 %, entry 2). Further reducing the PTSA equivalence to 6 % slightly improved the yield to 95 % (entry 3). However, a blank test without PTSA yielded only 51 % even after 17 h (entry 4). This result could be due to the consumption of the produced allyl alcohol from diallylether into propanal, confirming the need for PTSA to prevent isomerization and target allylation reactions. Changing PTSA with more convenient or recyclable acids, such as methanesulfonic acid or Amberlyst as solid acid led to unsuccessful reactions (entries 5 and 6).

Using experimental conditions detailed in Table 2 (entries 2 and 3), kinetic studies were performed in order to evaluate the impact of PTSA concentration on the evolution of the components in the reaction mixture (Figure 3). These experiments were conducted with 10 mmol of substrate **1a** to guarantee samplings, what could lead to slight differences in results in comparison to Table 2. With 26 % PTSA in the reaction medium, cyclohexane carboxaldehyde **1a** was almost fully converted into product **3a** in 600 minutes. In this configuration, very limited amounts, below 3 %, of propanal were detected. Interestingly, reducing the amount of PTSA to 6 mol% resulted in a faster reaction rate, requiring only 180 minutes to reach a maximum yield into **3a** of 92 %. On the other hand, a large number of by-products, such as propanal, were formed until the diallylether was completely converted.

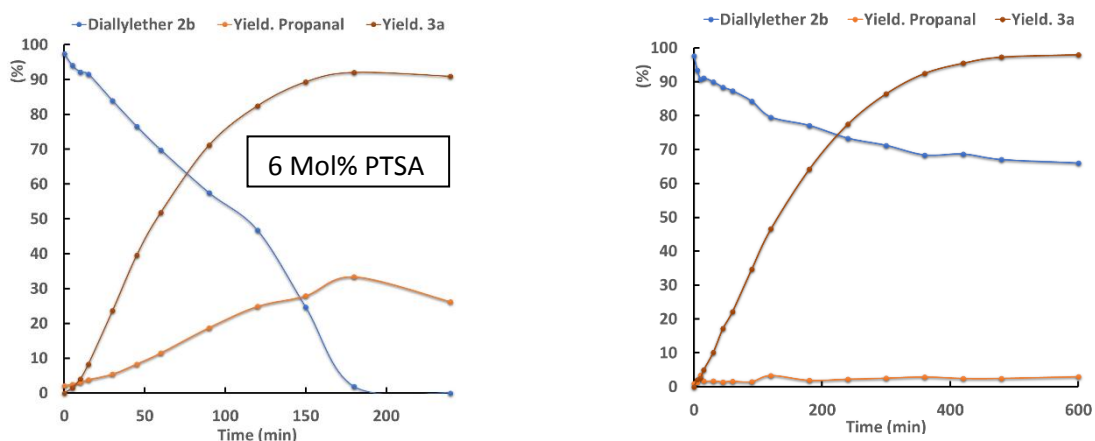


Figure 3. Evolution of conversions/yields in the different products during the α -allylation of carboxaldehyde cyclohexane **1a** with diallylether **2b**.

Conditions: carboxaldehyde cyclohexane **1a** (10 mmol), diallylether **2b** (20 mmol), $[\text{RuCpCl}(\text{PPh}_3)_2]$ (1 mol%), AgOTs (3.6 mol%), toluene : 2.5 mL, 60 °C.

During aldehydes allylation reaction, PTSA inhibited isomerization of allyl alcohol **2a** formed as by-product from diallylether **2b** but at the expense of a lower reaction rate. To limit the use of the allylating agent in excess, it is preferred to maintain a high concentration in PTSA. Modification of the catalytic complex could also limit propanal production by blocking the catalyst's ability to isomerize allyl alcohol without reducing its activity in aldehydes allylation. We thus evaluated different ligands in that reaction. Bridged diphosphines as dppe, dppb or dppf were chosen and ruthenium complexes were first synthesized by exchange between PPh_3 and the diphosphine [25,26]. These catalysts did not generate isomerization products during the allylation of cyclohexane carboxaldehyde **1a** with the optimized reaction conditions. However, these catalysts led to lower **3a** yields, 58, 72 and 50 % respectively, showing less activity towards the allylation of aldehydes (Figure 4). These catalysts are therefore not attractive considering the fact that they also required an additional synthesis step.

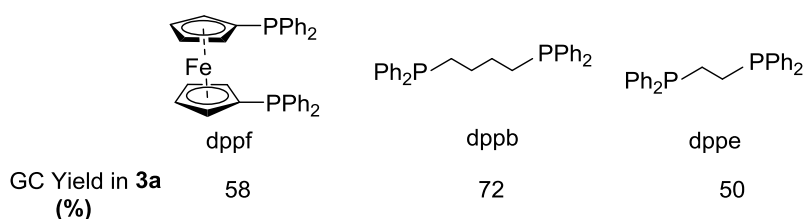


Figure 4. Ligands used in the Ru-catalyzed allylation of cyclohexane carboxaldehyde **1a** and GC yield in **3a**.

Conditions : cyclohexane carboxaldehyde **1a** (2 mmol), diallylether **2b** (4 mmol), $[\text{RuCpCl}(\text{PPh}_3)_2]$ (1 mol%), AgOTs (3.6 mol%), PTSA (26 mol%), toluene : 0.5 mL, 60 °C, 3 h.

Under the optimized conditions thus established (Ru catalyst, PTSA 26 % and diallylether **2b** as allylation agent), the allylation of various α -branched aldehydes was examined (Figure 5). These more hindered aldehydes than linear aldehydes are much less prone to participate in self-condensation reactions which is detrimental to the reaction selectivity. Results are reported in Table 3.

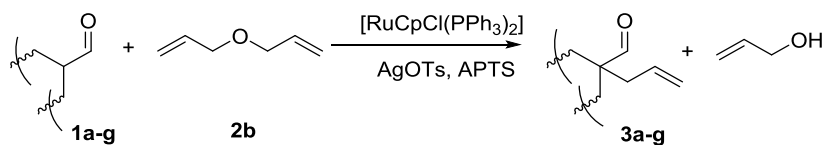
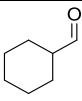
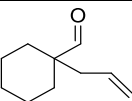

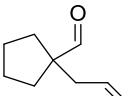

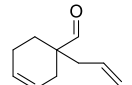
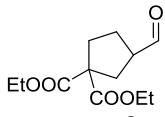
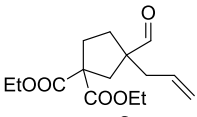
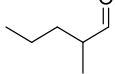
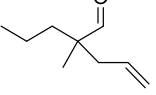
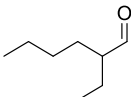
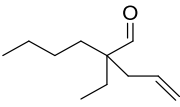
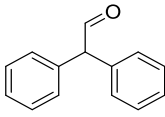
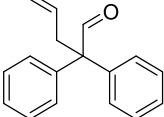


Figure 5. Ru-catalyzed allylation of α -branched aldehydes **1a-g**.

Table 3. Ru-catalyzed allylation of α -branched aldehydes **1a-g**.^{a)}

Entry	Aldehyde	Conv. 1a-g (%)	Product	Yield 3a-g (%) ^{b)}	a)	A
1		1a 99		3a 70	I d e h y d e 1 a - g (4 m m o l) , d i a l l y	A
2		1b 99		3b 60		
3		1c 97		3c 80		
4		1d 95		3d 44		
5		1e 99		3e 95		
6		1f 99		3f 79		
8		1g 99		3g 95		

lether **2b** (8 mmol), PTSA : 26 %, [RuCpCl(PPh₃)₂] (1 mol%), AgOTs (3.6 mol%), toluene : 1 mL, 60 °C, 17 h.

b) Isolated yield after chromatography column.

Reaction of different cyclic (**1a-d**) or linear (**1e-g**) α -branched aldehydes with diallylether **2b** provided very good conversions of at least 95 %. The corresponding α -allylated products **3a-g** were obtained with moderate to high isolated yields (44-95 %). No secondary products were observed in GC, but the difference between the conversions and the yields isolated can be explained by the purification stage, particularly with regard to the oxidation of the aldehyde function over time under air atmosphere. As expected, no isomerization of allyl alcohol was observed in that conditions.

We then turned our attention towards the linear aldehydes which have been poorly studied in literature because of the possibility of the self-aldol condensation of the substrate. We choose

valeraldehyde **1h** as model substrate (Figure 6). Interestingly, the product of monoallylation is a precursor of valproic acid which is widely used as antiepileptic drug and mood stabilizer [27,28].

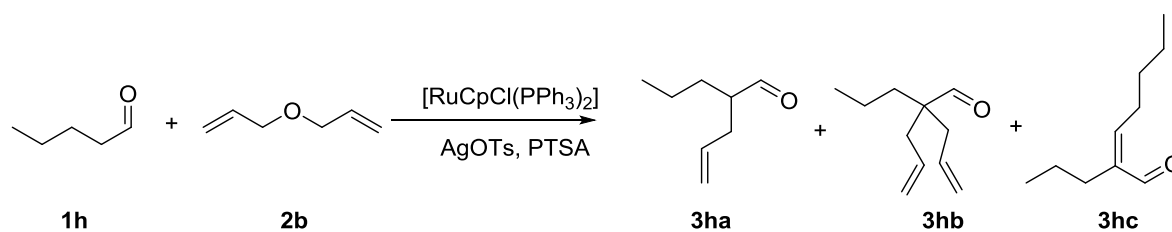


Figure 6. Ru-catalyzed α -allylation of valeraldehyde **1h**.

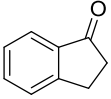
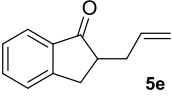
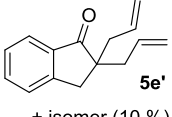
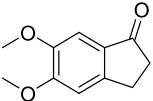
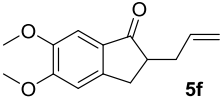
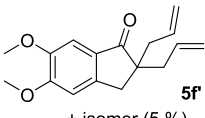
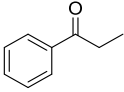
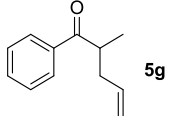
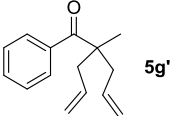
Table 4. Ruthenium catalyzed allylation of valeraldehyde **1h**.^{a)}

Entry	Eq nb. 2b	PTSA (mol%)	Conv. 1h (%)	Yield 3ha (%) ^{b)}	Yield 3hb (%) ^{b)}	Yield 3hc (%) ^{b)}
1	2	26	100	7	1	92
2	6	26	100	16	15	69
3	2	10	100	11	29	60
4	2	6	75	12	43	20
5	2	3	30	9	21	0
6	2	0	9	5	2	2
7	4	6	90	20	63	7

a) Valeraldehyde **1h** (2 mmol), $[\text{RuCpCl}(\text{PPh}_3)_2]$ (1 mol%), AgOTs (3.6 mol%), toluene : 0.5 mL, 60 °C, 3 h.

b) Determined by GC analysis using dodecane as internal standard.

As shown in Table 4, under the precedent optimized reaction conditions, valeraldehyde **1h** and diallylether **2b** reacted to provide a mixture of the allylvaleraldehyde **3ah** and diallylvaleraldehyde **3hb** along with the aldolisation/crotonisation product **3hc** as highly major product (92 %) (entry 1). To improve the yield in favor of **3ha** or **3hb**, the influence of quantity of diallylether **2b** was examined. 6 equivalents **2b** versus **1h** led to a decrease of the condensation product in favor of allylated products but condensation remained major with 69 % yield (entry 2). Under these acidic conditions, secondary aldolisation/crotonisation appeared to be favored over the allylation reaction. As seen in the optimization step, decreasing PTSA was studied to improve the allylation rate compared to condensation rate. As PTSA was decreased from 26 to 3 % (entries 1, 3-5), the aldolisation/crotonisation reaction was gradually prevented up to be suppressed with 3 % of acid but in that latter case, valeraldehyde conversion dropped to 30 % (entry 5). Reaction of valeraldehyde without PTSA afforded a very low 9 % conversion to the

5		4e	100		5e	 + isomer (10 %)	5e : 34 5e' : 40	a) K e t o
6		4f	85		5f	 + isomer (5 %)	5f : 51 5f' : 18	
7 ^{c)}		4g	22		5g		5g : 7 5g' : 6	

ne **4a-g** (4 mmol), diallylether **2b** (8 mmol), PTSA : 26 %, [RuCpCl(PPh₃)₂] (1 mol%), AgOTs (3.6 mol%), toluene : 1 mL, 60 °C, 17 h.

b) Isolated yield after chromatography column. c) Yields determined by GC using dodecane as internal standard.

The reaction mixture obtained from cyclohexanone **4a** proved to be complex with the formation of numerous products (from mono to tetra allylated products) which could not be isolated. The major product in the case of α -tetralone **4b** was the monoallylated derivative (58 %) in mixture with the diallylated one (16 %). With the α -branched tetralone **4c**, only monoallylation could take place and the corresponding product was obtained with 31 % isolated yield. Interestingly, the β -tetralone **4d** led to the exclusive formation of the diallyl product. This shows the important role of the phenyl group as stabilizing group and allows to propose that the ketone reacts via its enol which is particularly stabilized in β -tetralone. We have also evaluated indanone **4e** and 5,6-dimethoxyindanone **4f**. The electrodonor group methoxy seemed to decrease the reaction rate with a higher proportion of the mono allylated product in the reaction mixture. Notably, in the cases of **4b**, **4e** and **4f** substrates, in addition to the diallylproducts **5b'**, **5e'** and **5f'**, NMR spectra showed the presence of others disubstituted products with yields of 5, 10 and 5 % respectively. In these compounds, an allyl group has been isomerized in 2-propenyl as evidenced by ¹H NMR analysis (see Supporting information). We think that isomerization of the terminal double bond took place on the monoallyl products before the second allylation. This hypothesis has been confirmed experimentally: no isomerization of the diallyl products was observed after several days in the reaction conditions.

We currently proposed a mechanism of the reaction (Figure 9).

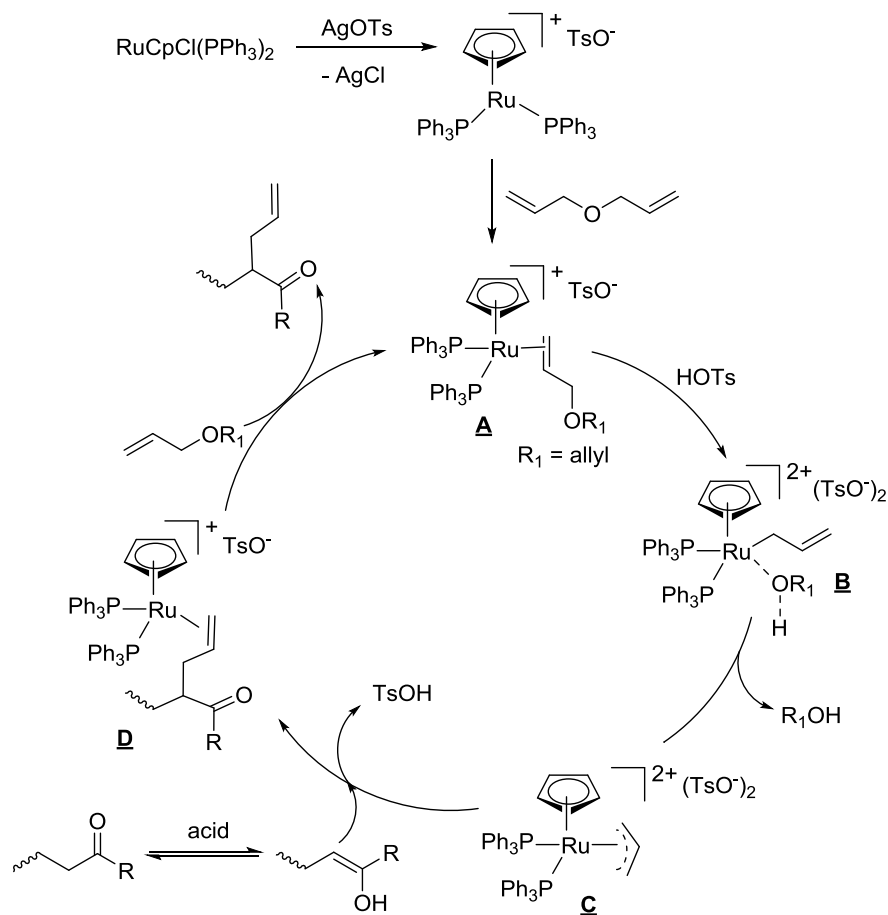


Figure 9. Proposed mechanism for the ruthenium catalyzed allylation on carbonyl compounds.

The cationic ruthenium complex $[\text{RuCp}(\text{PPh}_3)_2]^+ \text{TsO}^-$ was first obtained by reaction of the precursor $\text{RuCpCl}(\text{PPh}_3)_2$ with AgOTs . Reaction of diallylether with the ruthenium complex $[\text{RuCp}(\text{PPh}_3)_2]^+ \text{TsO}^-$ led to the intermediate **A** $[\text{RuCp}(\text{PPh}_3)_2(\text{diallylether})]^+ \text{TsO}^-$ in which diallylether is coordinated with its olefin moiety. By protonation of the alkoxy group in the complex **A** with TsOH , oxidative addition of the ether could occur leading to the $[\text{RuCp}(\text{PPh}_3)_2(\sigma\text{-allyl})]^{2+} (\text{TsO}^-)_2$ **B** intermediate. After elimination of alcohol, **B** is rearranged to the π -allyl intermediate **C**. Nucleophilic attack of the enolate on the π -allyl ligand led to the Ru-allylated complex **D**. The final product is obtained after dissociation of the final product and coordination of diallylether with regeneration of the active species **A**.

5. Conclusions and Future Perspectives

In summary, we have developed the α -allylation of aldehydes and ketones compounds with allyl alcohol or diallylether. The reaction is promoted by ruthenium catalyst $[\text{RuCp}(\text{PPh}_3)_2]^+\text{TsO}^-$ generated in situ from the reaction between $[\text{RuCp}(\text{PPh}_3)_2\text{Cl}]$, a simple air stable precursor and AgOTs. The reaction has been optimized with cyclohexane carboxaldehyde as model reagent. Allyl alcohol is efficiently reacted, still, diallylether proved to be the allylating agent of choice for that reaction and afforded almost quantitative yields in allylated derivatives. The efficiency of the reaction is due to the use of PTSA as an acid which prevents the ruthenium-catalyzed isomerization of allyl alcohol in propanal. Thanks to the optimized protocol, the process could be successfully applied to the transformation of α -branched aldehydes. With the same reaction conditions, linear aldehydes led mainly to the product of self-aldol condensation. It is noteworthy that with a judicious choice of the reaction conditions, allylated aldehydes could be formed as major products as a mixture a mono- and diallylated derivatives. The protocol is not restricted to aldehydes and ketones have also been reacted. Cyclic ketones afforded mixtures of mono- and diallylated derivatives that can be separated by column chromatography. Efforts are underway to develop new catalytic systems allowing the allylation of linear aldehydes with an improvement of the selectivity of the reaction toward the monoallylated α -aldehyde.

CRedit authorship contribution statement

Aurélien Béthegnies, Clément Dumont, Mathieu Sauthier: Conceptualization, methodology and investigation; **Anthony Saint Pol** and **Bouchaib Mouhsine:** Synthesis and catalysis, **Aurélien Béthegnies, Mathieu Sauthier:** writing—original draft preparation, **Mathieu Sauthier:** review and editing.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Supplementary Materials

Supplementary data associated with this article can be found in the online version at:

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