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Homogeneous Chemoselective Hydrogenation of Heterocyclic Compounds – The Case of 1,4 Addition on Conjugated C-C and C-O Double Bonds of Arylidene Tetramic Acids

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Additional information is available at the end of the chapter

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1. Introduction

Homogeneous hydrogenation constitutes an important synthetic procedure and is one of the most extensively studied reactions of homogeneous catalysis. The impressive development of coordination and organometallic chemistry has allowed for the preparation of a wide variety of soluble metal complexes active as homogeneous hydrogenation catalysts under mild conditions. [1,2]

Early advances in chemoselective olefin hydrogenation were dominated by the introduction of homogeneous transition metal complexes. [3-5] Many of them allow for the preferential reduction of carbon-carbon double bonds over a coexisting C=O functionality. [6-11]

Catalysis is a multidisciplinary scientific concept that serves a broad range of industries covering specialty, fine, intermediate, commodity and life science chemicals. Catalysts are commonly used for the hydrogenation of alkenes, alkynes, aromatics, aldehydes, ketones, esters, carboxylic acids, nitro groups, nitriles and imines. These materials may be in the form of bio-, homogeneous, heterogeneous and heterogenised homogeneous catalysts where each type has its own special properties that can be adjusted for their optimal use. The trend is towards selective hydrogenation of specific groups of a fine chemical, leaving all other structural groups and activated sites intact. This is of great importance for the medicinal industry. Although the enantioselective hydrogenation of C=C and C=hetero-atom double bonds lays mostly in the field of homogeneous catalysis,

intensive research has led to the use of heterogeneous reactions for those applications. There have been some examples identified, where heterogeneous catalysts show promising results. [12]

The catalytic hydrogenation of α,β -unsaturated ketones in particular has been widely investigated. This unsaturated system is encountered in many organic structures linear or cyclic. Literature reports the use of heterogeneous catalysts, in addition to homogeneous catalysts. Therefore, it is essential to investigate all relative findings in the area of heterogeneous catalysis, along with homogeneous catalysis to reveal the possibilities for chemoselective and regioselective hydrogenation of conjugated and non-conjugated unsaturated systems.

The implementation of the $H_4Ru_4(CO)_9[(S)\text{-BINAP}]$ complex in the process allows for wide range of possibilities. This versatile four-Ru-nuclei complex is a potential hydrogenation agent, but could as well catalyze a number of undesired side-reactions that need to be avoided. Past reviews have indicated ruthenium as a transition metal with many possibilities depending on the environment provided. [13] Transformations including additions, redox isomerizations, coupling reactions and cycloadditions can be achieved using the appropriate ligands and reaction conditions. On the other hand, a large number of ligands has been developed and tested for their performance in asymmetric hydrogenation. [14] Ligands of particular interest are phosphorus ligands and more specifically phosphane and phosphine ligands (Figure 1), not neglecting the value of phosphonate and phosphinite ligands. [15] In any case, we need to focus on selectivity (enantioselectivity, chemoselectivity, regioselectivity, etc.) for reasons of economy. The word economy does not only refer to substrate or catalyst economy, but also to atom economy. What is demanded today is a process as clean as possible, from which we derive the desired product only, limiting or even extinguishing all byproducts.

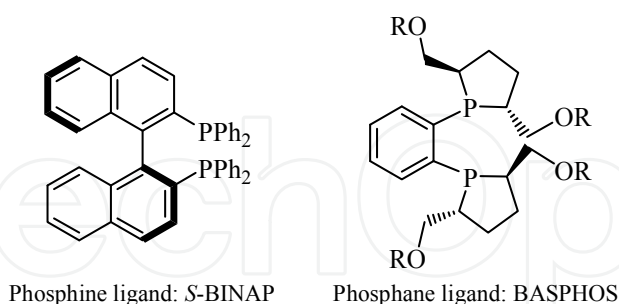


Figure 1. Examples of phosphorus ligands for enantioselective hydrogenation.

Arylidene tetramic acids present high structural versatility. The pyrrolidine-2,4-dione nucleus ring can be substituted by a variety of functional groups, incorporating either electron donating or withdrawing characteristics. It is found that 3,5-bisarylidene tetramic acids can be synthesized in high yields, providing a very good and versatile substrate for the catalytic hydrogenation. [16] This multi-conjugated structure includes an α,β -unsaturated ketone built in the heterocyclic nucleus, that is possible to be subjected to hydrogenation, as it is depicted in Figure 2.

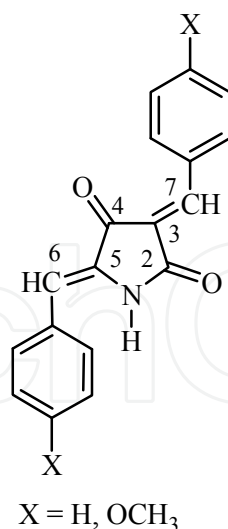


Figure 2. 3,5-Bisarylidene tetramic acids.

This unsaturated carbon backbone structure can be divided in sections that exhibit interpretable characteristics. So, we can distinguish two aromatic monoenes (C7-arylidene and C6-arylidene groups) and three α,β -unsaturated ketones (C2=O-C3=C7, C4=O-C3=C7 and C4=O-C5=C6 groups). Of course, the extended conjugated structure through the aromatic rings cannot be neglected; however, for reasons of simplicity we will regard this system as an addition of several simple antagonistic unsaturated systems. So, it is clear that we need to investigate the behavior of different unsaturated systems and their antagonistic action in conditions of catalytic hydrogenation if we are to discover the processes involved in the hydrogenation of 3,5-bisarylidene tetramic acids.

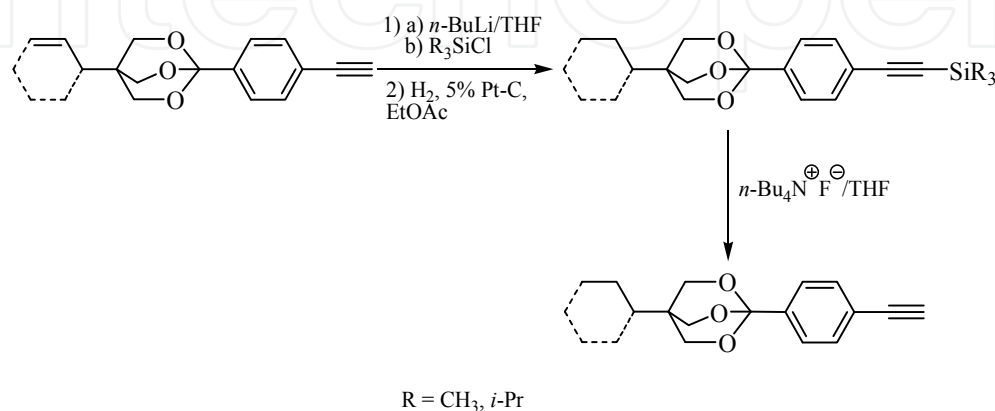
2. On the hydrogenation of conjugated and non-conjugated olefins

The most common form of a conjugated system is that of conjugated dienes. Indeed, the most common conjugated system, 1,3-butadiene, was discovered in the early 20th Century and since then it has been widely investigated. Aromatic monoenes, and furthermore monoenes are also very important, as they comprise a similar to the conjugated dienes substrate activity towards catalytic hydrogenation. The case of α,β -unsaturated ketones is more complex and will be dealt with later in the text. Economics of the hydrogenation process lead to the preferential employment of heterogeneous metal catalysts, since the benefits against the homogeneous catalysts are multiple:

- Cheaper transition metals.
- Cheaper supporting materials.
- Easier to recycle and regenerate.

On the other hand homogeneous catalysts are usually more selective and can be specifically modified to meet the needs for a particular substrate application. This will be further discussed later in the chapter. It is also possible to heterogenize an homogeneous catalyst, compromising with a partial loss of activity.

The competitive addition of hydrogen in the case of non-conjugated double and triple C-C bonds has been studied in the past. [17] It has been found that the hydrogenation of triple bonds, especially terminal triple bonds, is thermodynamically favorable compared to double bonds. In this case, protection of the ethynyl group by silylation of the 1-(4-Ethynylphenyl)-4-propyl-2,6,7-tioxabicyclo[2.2.2]octane, allowed for the selective hydrogenation of the olefinic bond, in moderate rates (Scheme 1). To achieve even higher selectivity immobilized platinum on carbon was employed, since platinum is known to favor the hydrogenation of olefins.



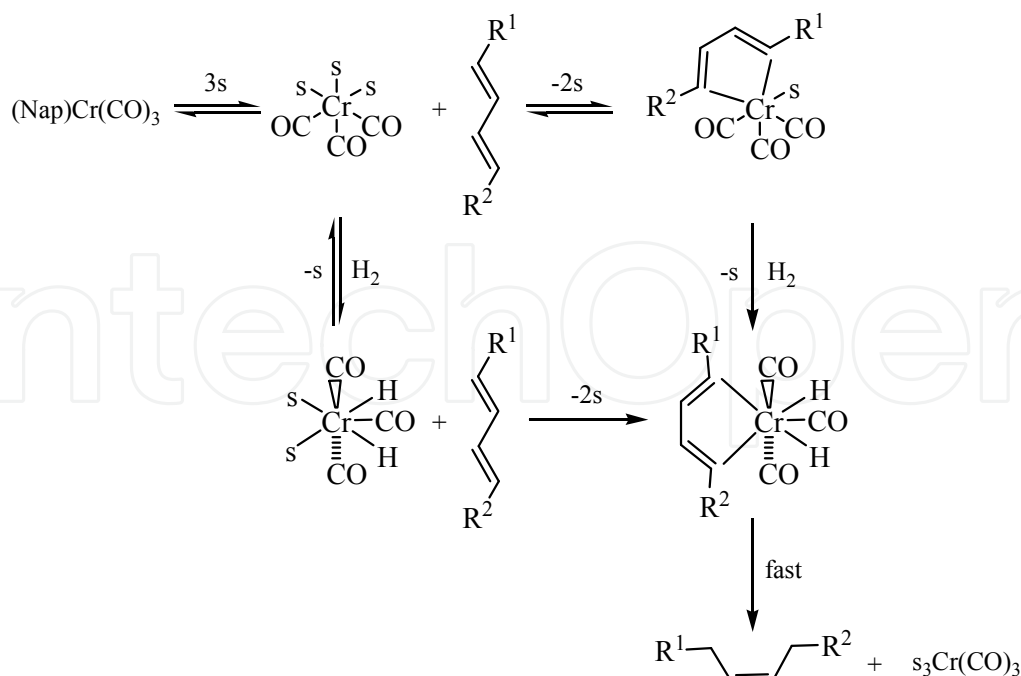
Scheme 1. Silylation and selective hydrogenation of the olefinic bond of 1-(4-Ethynylphenyl)-4-propyl-2,6,7-tioxabicyclo[2.2.2]octane.

Studies on the homogeneous catalytic hydrogenation of conjugated dienes and cyclic conjugated dienes point out the steric effects that can potentially inhibit the addition of hydrogen. [18] In particular, conjugated dienes where 1,4-hydrogenated using (Naphthalene)Cr(CO)₃ in atmospheric hydrogen pressure, room temperature and polar coordinated solvents. The observations include the following:

- Naphthalene is substituted by the solvent in the Cr complex.
- The hydrogenation follows 1st order kinetics at low concentration of substrate and catalyst.
- 1,4-trans substituted cyclic dienes experience steric effects which results in slow reaction rates.
- The rate determining step is the oxidative addition of hydrogen (isotope kinetic studies).
- Addition of free naphthalene in the solvent decreases the rate of hydrogenation (displaces solvent in the complex formation).

In Scheme 2, the proposed mechanism for the 1,4-hydrogenation is presented.

On the other hand, as Cho and Alper suggest, the application of oxygen-preactivated [(Bu₂PH)PdPBu₂]₂, a binuclear palladium complex, in the homogeneous hydrogenation of various olefin and unsaturated ketone dienes, leads to selective 1,2-hydrogenation. The process proceeds in good yields, under mild conditions and is effective in several cyclic compounds as well. [19]



Scheme 2. Hydrogenation mechanism for the 1,4-hydrogen addition on conjugated dienes (s = solvent).

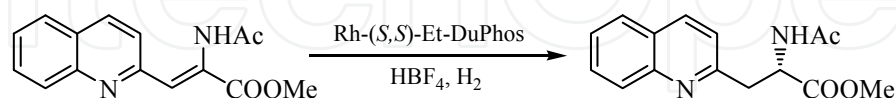
Similar results were observed during the study of the catalytic behavior of a dendrimer-bound PdCl_2 complex. [20] In this case, cyclopentadiene is hydrogenated in atmospheric oxygen, in a polar solvent (ethanol). This study clearly states the superior performance of polar solvents. The addition of hydrogen occurs only at one of the two conjugated double bonds, leading to a monoene (cyclopentene). No 1,4-hydrogenation is observed. Moreover, the hydrogenation rate is dramatically reduced after the cyclopentadiene is consumed and there is no cyclopentane formation observed.

Dahlén and Hilmersson proved that the employment of THF, a moderate polarity solvent along with the catalytic system of $\text{SmI}_2/\text{H}_2\text{O}/\text{amine}$, delivers high versatility and selectivity for the hydrogenation of C-C double and triple bonds. The process proceeds on a high rate and with mild conditions. Depending on the amine employed, different results can be obtained. [21] The main conclusions can be summarized as follows:

- Conjugated dienes are preferably hydrogenated, rather than non-conjugated dienes.
- Cyclic conjugated dienes are 1,2-hydrogenated (no 1,4-hydrogenation occurs).
- Linear or branched conjugated dienes afford a mixture of 1,2 and 1,4-hydrogenated products (still non-conjugated double bonds are not hydrogenated).

The possibility of the selective hydrogenation of non-conjugated dienes to monoenes was demonstrated by more recent studies. [22] The catalytic system of $\text{NiCl}_2\text{-Li-DTBB}$ (4,4'-di-*tert*-butylbiphenyl) in a polar ROH solvent, generates $\text{Ni}(0)$ nanoparticles and molecular hydrogen in situ. This enables the selective hydrogenation of cyclic, bi-cyclic and linear non-conjugated dienes to monoenes in mild, atmospheric conditions. Moreover, linear alkenes are completely saturated under these conditions. The system of $\text{NiCl}_2\text{-Li-DTBB}$ works efficiently with THF as well.

In the field of homogeneous catalysis a wide range of Ru and Rh catalysts has been developed. The most common type of ligand in these complexes is the phosphorus-based ligand. The application of these catalysts in enantioselective hydrogenation of olefins has proven to be successful throughout the last decades. The successful hydrogenation results cover many types of olefins, starting from α -Dehydroamino acid derivatives, enamides and (β -Acylamino) acrylates, to Enol esters (Scheme 3). Hydrogenation results are characterized mainly by the mild conditions applied, good enantiomeric excess and high yield. The solvents of choice are mainly MeOH, DCM, EtOH and THF. [15]



Scheme 3. DuPhos homogeneous catalytic hydrogenation of an α -Dehydroamino acid derivative.

3. The case of ketones

Ketones and unsaturated ketones are an important class of organic compounds since they are biologically active substances or precursors for the synthesis of biologically active substances. In many cases, the required process for the transformation of the precursor to the active derivative is the catalytic hydrogenation process. That is the reason why many researchers focus on the investigation of this process. To pronounce the importance of the catalytic hydrogenation of ketones we will refer to examples for both functionalized and unfunctionalized ketones, analyzing the hydrogenation conditions involved and the catalytic complexes employed. One interesting case is the Ru catalytic hydrogenation of aryl-pyridyl ketones to afford Carbinoxamine precursors. Carbinoxamine is an important histamine H_1 antagonist (Figure 3). The Ru complex employed (Figure 3) is very effective especially when the solvent of the reaction is polar (MeOH, EtOH), but best results are derived with 2-propanol in terms of high yield and enantioselectivity (up to 98% e.e.). The reaction conditions are mild and the reaction scheme is presented in Scheme 4. [23]

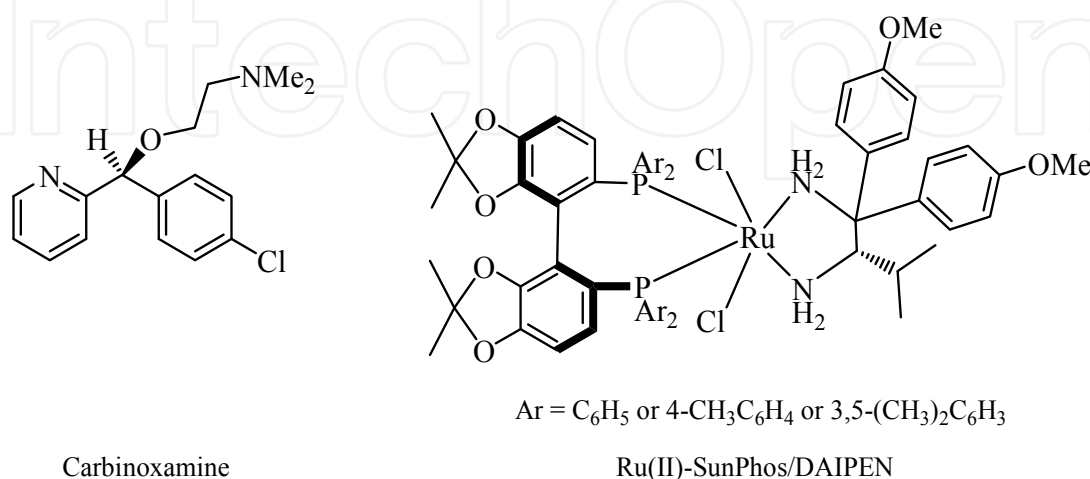
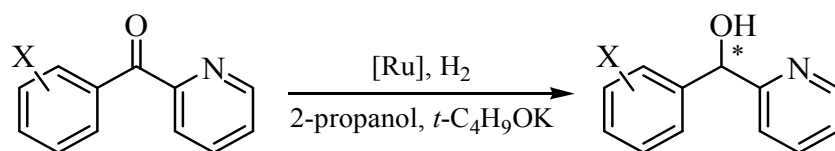


Figure 3. Carbinoxamine, an histamine H_1 antagonist and the catalyst Ru(II)-SunPhos/DAIPEN.



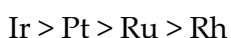
X = CH₃, CH₃O, F, Cl, Br

Aryl-Pyridyl Ketone

Scheme 4. Catalytic hydrogenation of a substituted aryl-pyridyl ketone with Ru(II)-SunPhos/DAIPEN.

The electron density of the central metal of the catalytic system employed has a major contribution in the overall hydrogenation process, since it enables the intermediate hydride formation. [24] Spogliarich et al. showed that Ir complexes present high selectivity in the hydrogenation of conjugated enones. The selectivity is even higher if there is an olefinic bond substitution by an aromatic group. It seems that electron withdrawing groups favor the reduction of the carbonyl group, as it happens when employing Ru catalysts, in hydrogen transfer hydrogenation reactions. In a similar study Spogliarich presented an analogous behavior in the homogeneous catalytic hydrogenation of cyclic conjugated enones with Ir complexes. [25]

V. Ponec investigated in a series of studies the behavior of carbonyl compounds subjected to hydrogenation. In the original study the competitive hydrogenation of acetone and propanal is investigated. [26] The system Pt/SiO₂ is employed, promoter-free or promoted by Ga, Ge or Fe compounds. The conditions involve a seldom encountered continuous flow glass reactor, atmospheric temperature and pressure and ethanol as solvent. It is clear by this study that pure Pt preferably catalyzes acetone hydrogenation, whereas doped Pt works better with propanal, with high selectivity. Pd provides very poor results when employed for the hydrogenation of carbonyl compounds, when at the same time presents very low self poisoning effects. When a mixture of acetone and propanal is subjected to hydrogenation certain observations occur. Propanal is much more strongly adsorbed than acetone, affording very low hydrogenation rates. On the other hand, in homogeneous catalysis propanal is more readily hydrogenated. [27] In a more extended work, Ponec denotes the role of ionic admixture to metal/support catalysts for the selective hydrogenation of the carbonyl group of α,β -unsaturated aldehydes. Focusing on the mechanism of catalysis on such conjugated systems, Ponec suggests an 1,4 adsorption of the unsaturated aldehyde over Pd, that ultimately lowers the selectivity towards C=O hydrogenation. Promoters may induce ensemble effects that minimize the electronic (ligand) effect and favor the hydrogenation of the C=O group. Other mechanism suggestions for the promoter effect involve the modification of the surface composition of the support, the particle size morphology and 'chemical' promotion, like the electrostatic field promotion which changes the field on and occupation of the orbitals mediating the metal-O or metal-C bonds. Regarding the selectivity in reducing carbonyl groups, the platinum-group metals can be ranked according to their selectivities as follows:



It is established that application of Sn, Ga, Ge or Fe promoters may enhance the effectiveness of these metals by activating the oxygen of the carbonyl group. The activation involves the formation of a chemical bond between the oxygen and the cation of the promoter. The material used as a catalyst support is another important parameter. TiO_2 is identified as an excellent support promoting the $\text{C}=\text{O}$ hydrogenation. [28]

A different approach by Kazuyuki H. et al. showed that the system Pd/C(en) , that is expected to be a poor hydrogenation catalyst for single or conjugated ketones, functions rather well with aromatic ketones. [29] This is a mild hydrogenation reaction that takes place in atmospheric conditions. A very important result is derived from this study. The key factor to control the selectivity of the hydrogenation and avoid any undesirable hydrogenolysis on the substrate is to employ THF as a solvent rather than a polar solvent, such as MeOH. This is most important if bis-aromatic ketones are subjected to hydrogenation.

A highly chemoselective and regioselective homogeneous catalytic hydrogenation of unsaturated aldehydes and ketones to unsaturated alcohols is achieved by Jian-Xin Chen et al. employing a binuclear-bidendate Phosphine-Copper(I) hydride complex (Figure 4). [30] The mechanism involves the initial fragmentation of the Cu dimer to functional monomers. THF, or the system benzene/*t*-butanol are the preferred solvents and a major observation is that a higher hydrogen pressure (above 70psi) inhibits the catalyst's functionality. High chemoselectivity is achieved for cyclic and aromatic ketones. However, 1,2 hydrogenation of α,β -unsaturated aldehydes and ketones requires a higher hydrogen pressure (above 1atm), and benzene/*t*-butanol as a solvent system. Also, it is not sufficiently regioselective, affording a mixture of hydrogenated products.

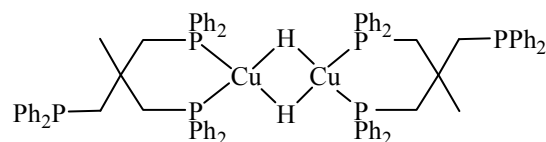
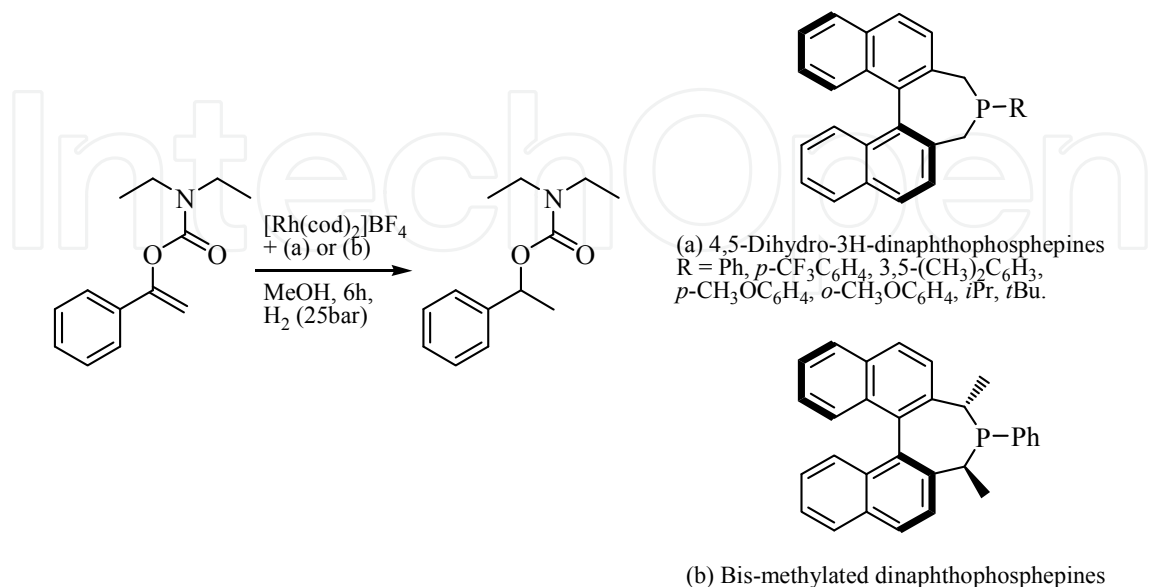


Figure 4. Binuclear-bidendate Phosphine-Copper(I) hydride complex: $[(\eta^2\text{-tripod})\text{CuH}]_2$, tripod = 1,1,1-tris (diphenylphosphinomethyl)ethane).

In another application of a phosphine monodendate (based on 4,5-dihydro-3*H*-dinaphthophosphepines), with Rh nucleus this time, very good enantioselectivity was derived for the homogeneous hydrogenation of enol carbamates, as presented by S. Enthaler et al (Scheme 5). [31] Very high enantioselectivities are achieved, up to 96% e.e. The optimization study reveals a moderate effect of the temperature and hydrogen pressure to the hydrogenation and enantioselectivity result. The solvents with the best behavior are the polar ones (methanol and ethanol). However, a rather high value of hydrogen pressure (25bar) is derived as optimal. Furthermore, due to ligand dissociation the temperature cannot be well elevated above 90°C.

An alternative to copper hydrides is presented by N. Ravasio et al. [32] This alternative involves the system Cu/SiO_2 and is employed for the hydrogenation of α,β -unsaturated

ketones. The reaction conditions are quite mild and the overall performance shows good selectivity. In fact, this catalyst affords only saturated ketones, in both cyclic and linear structures. The only handicap is the use of toluene as a solvent.

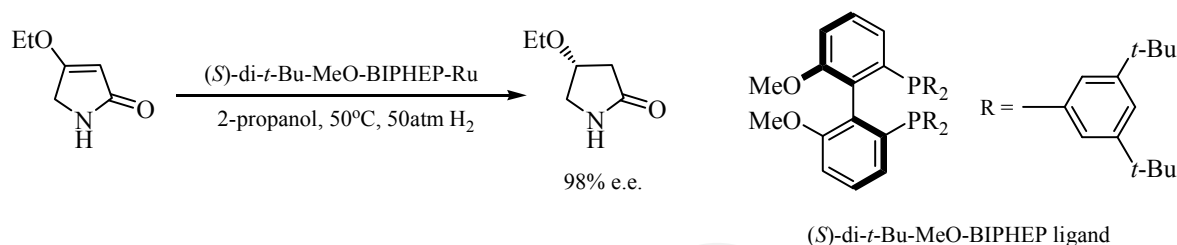


Scheme 5. Substituted dinaphthophosphepines homogeneous hydrogenation of enol carbamates.

Two separate studies investigate the application of the more expensive gold/support systems. [33,34] Gold is supported either on Fe₂O₃ or Al₂O₃, in different weight percentage and different particle size. Depending on the catalyst there is a differentiation in the selectivity during the hydrogenation of α,β -unsaturated ketones. Usually, a mixture of a saturated ketone and unsaturated alcohol is derived, with only a small percentage of saturated alcohol. XRD diffraction pattern also reveals low temperature reduction of amorphous iron by the attached gold, to form magnetite (Fe₃O₄). These studies confirm that the major role in the hydrogenation selectivity is played by the support, and more particularly the reducibility of the support. Reduced Fe₂O₃ increases the electron density of the gold particles, increasing the selectivity towards C=O reduction.

So far, we mostly encounter high selectivities for the hydrogenation of the C=O group of α,β -unsaturated ketones. The reverse selectivity may be obtained with the application of a Ruthenium heterogeneous catalyst. [35] The Ru catalyst is employed in the form of Ru nanoparticles immobilized on hectorite. The use of ethanol as solvent and moderate hydrogen pressure (1-10 bar) at room temperature ultimately affords saturated ketones, with a selectivity over 99%. Common substrates are 3-buten-2-one and 3-penten-2-one. The highest benefit is the possibility to recycle and reuse the hectorite-supported Ru nanoparticles.

Phosphorus ligand homogeneous catalysts present very poor enantioselectivity results when it comes to α,β -unsaturated ketones, lactams, amides and carboxylic acid esters. However, a successful attempt on the hydrogenation of 3-ethoxy pyrrolidinone with a dicationic (*S*)-di-*t*-Bu-MeO-BIPHEP-Ru complex in 2-propanol is reported (Scheme 6).



Scheme 6. [Ru] homogeneous enantioselective catalytic hydrogenation of 3-ethoxy pyrrolidinone.

In the case of α -, β - and γ -ketoesters as well as amino ketones, homogeneous chiral Ru catalysts are quite effective, even though the reaction times are prolonged. In the case of unfunctionalized ketones (aromatic ketones, aliphatic ketones, unsaturated ketones) homogeneous Ru catalysts presented low selectivity towards the C=O bond. It was Noyori's catalyst *trans*-[RuCl₂(diphosphane)(1,2-diamine)] that first enabled the enantioselective hydrogenation of C=O double bond of α , β -unsaturated ketones and cyclic enones. [15]

Unfunctionalized ketones, and more specifically aromatic ketones, were investigated by Xu et al. [36] The research group discovered that a Ru(II) catalyst containing the BINOL backbone (Figure 5a) is able to successfully hydrogenate a wide range of aromatic ketones, with high yields and up to 99% e.e. All reactions are conducted in 2-propanol. Later, a variation of this amino-phenyl catalyst (Figure 5b) was adopted by Arai et al. for the catalytic hydrogenation of α -branched aromatic ketones. High enantioselectivities and diastereoselectivities are achieved in mild reaction conditions even for the hydrogenation of racemic α -amido ketones. The solvent of choice is 2-propanol. [37]

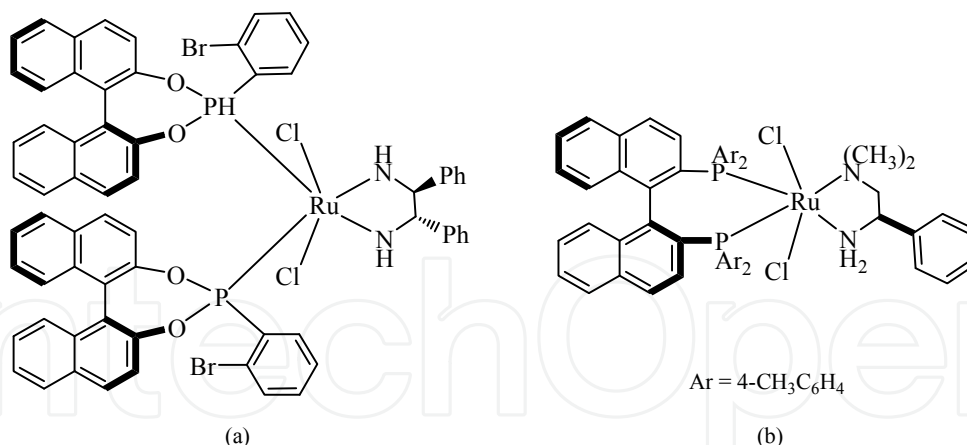
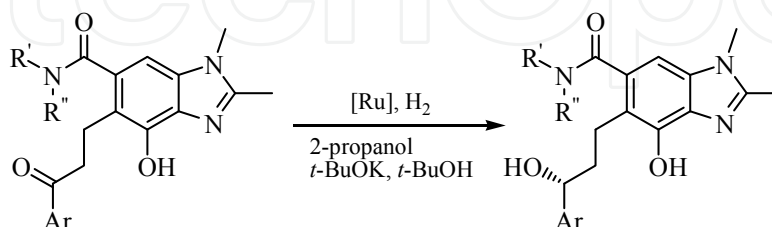


Figure 5. (a) Ru(II)-BINOL and (b) Ru(II)-TolBINAP/DMAPEN catalysts for the hydrogenation of aromatic ketones.

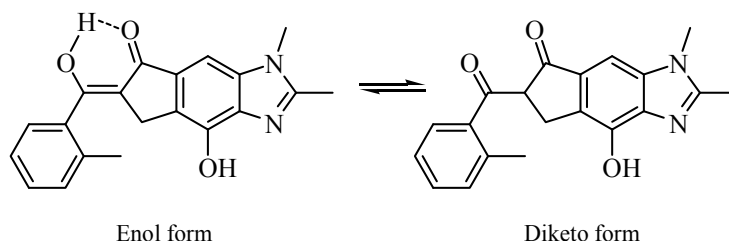
Another study on the hydrogenation of aromatic ketones employs complexes Ru(II)-TunePhos/DPEN and Ru(II)-TunePhos/DAIPEN which are similar to Ru(II)-TolBINAP/DMAPEN. [38] These catalytic complexes are proven very efficient for the hydrogenation of a wide range of unfunctionalized ketones. Yields and enantioselectivities are always over 80% and the conditions are quite mild, with the exception of the elevated hydrogen pressure (10-50bar). The solvent of choice is 2-propanol.

Another ketone hydrogenation application for a R(II)-DAIPEN complex is for the synthesis of 3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazoles. The full structure of the catalytic complex this time is: RuCl₂[Xyl-P-Phos][DAIPEN]. The hydrogenation reaction is depicted in Scheme 7. This process exhibits high selectivity. However, it requires elevated temperature and pressure conditions to afford good yields (50-80°C and 30-80bar). Rh and Ru catalysts are tested, with various ligands. Best results are derived with the Noyori-type complex RuCl₂[Xyl-P-Phos][DAIPEN], that affords 100% yield with over 90% e.e. The solvent of choice is 2-propanol with 1M solution of *t*-BuOK in *t*-BuOH. [39]



Scheme 7. RuCl₂[Xyl-P-Phos][DAIPEN] catalytic hydrogenation of ketones for the synthesis of imidazole derivatives.

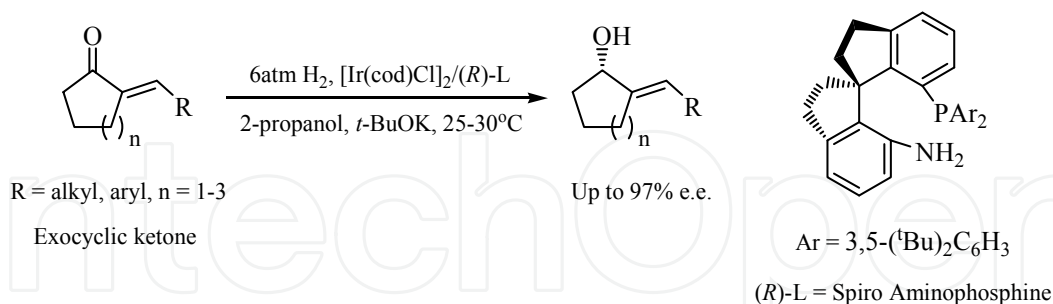
Another interesting result from the same research is the keto-enol tautomerism that is observed in one of the hydrogenation byproducts (Scheme 8). The conclusions derived are that keto-enol tautomers are very common in the case of exocyclic ketones, and that the formation of significant byproducts cannot be avoided even under thoroughly controlled reaction conditions.



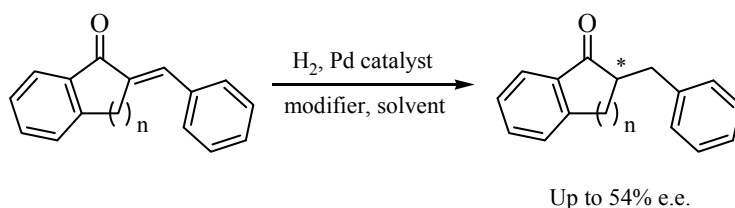
Scheme 8. Keto-enol tautomerism of the byproduct formed during the Scheme's 5 hydrogenation.

Exocyclic ketones can be catalytically hydrogenated to afford chiral cyclic alcohols which are important intermediates for the synthesis of a variety of biologically active molecules. In particular, the catalytic hydrogenation of exocyclic α,β -unsaturated ketones enables the synthesis of exocyclic allylic alcohols (Scheme 9). Xie et al. employed an Ir catalyst (Scheme 9) to achieve this hydrogenation in 2-propanol/*t*-BuOK. The results are remarkable, with a yield over 95% and e.e. over 90%. [40] Earlier, Fogassy et al. attempted to achieve the hydrogenation of differentiated exocyclic α,β -unsaturated ketones (Scheme 10) using the heterogeneous catalytic system Pd/TiO₂/cinchonidine and various polar and non-polar solvents. Pd is recognized as a poor C=O hydrogenation catalyst and the activity is directed towards the C=C double bond. Additionally, the presence of TiO₂ substrate and the cinchonidine promoter enhances the functionality and enantioselectivity of the catalyst. Still, the enantiomeric excess of the product reported by Fogassy et al. is not higher than 54%. [41]

In total, we have described two different hydrogenation methods for exocyclic α,β -unsaturated ketones, which selectively hydrogenate different unsaturated centers.



Scheme 9. Exocyclic ketone catalytic hydrogenation with the homogeneous [Ir(cod)Cl]₂/(R)-L catalyst.



Scheme 10. Catalytic heterogeneous hydrogenation of the C=C double bond of exocyclic α,β -unsaturated ketones with Pd/supported modified catalysts.

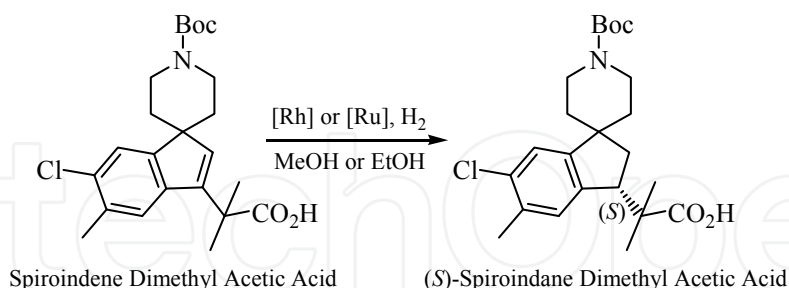
After this in depth investigation of the hydrogenation of ketones, given the fact that is a field with the most important advances over the last years, we have to pay attention to the heterocyclic compounds. Indeed, the presence of a carbonylic group in the ring of an heterocyclic compound changes completely the behavior of the C=O double bond. Few advances were made in that field and an insight of this process will reveal the complexity that is hidden in the structures of heterocyclic compounds.

4. Hydrogenation of heterocyclic compounds

Heterocyclic compounds are in general more versatile than cyclic or linear organic structures. Electron distribution is largely unbalanced and there are strong intramolecular interactions because of the heteroatom presence in the backbone structure. Usually, it is hard to theoretically disassemble these structures into smaller functional groups to investigate their behavior, but sometimes it is the only way to interpret the experimentally observed results. In this paragraph we will refer to some characteristic examples of catalytic hydrogenation of heterocyclic compounds to emphasize the versatility of these structures.

He et al. successfully attempted to hydrogenate Spiroindene Dimethyl Acetic Acid to (S)-Spiroindane Dimethyl Acetic Acid (Scheme 11) using Rh and Ru asymmetric catalysts. Spiroindane and its analogues are potent MC4R antagonists and could be used as a treatment for obesity as well as erectile dysfunction. The hydrogenation reaction proceeds in mild conditions, and Ru is proven to be much more efficient compared to Rh when the same ligands are employed. The solvent of choice is ethanol and conversion reaches 100% in the

case of Ru, with good enantiomeric excess. Observing Scheme 11 we can understand that this is an aromatic-conjugated system with an attached heterocyclic ring.



Scheme 11. Catalytic hydrogenation of Spiroindene Dimethyl Acetic Acid to (*S*)-Spiroindane Dimethyl Acetic Acid.

Still, the selectivity is high and the extended unsaturated system is not an antagonist to the hydrogenation of the conjugated double bond. [42]

The system of substituted pyridines and quinolines (Figure 6) was investigated by Solladié-Cavallo et al. This is a complex heterocyclic and polyaromatic system, bearing a number of potential sites for catalytic hydrogenation. As the authors report, they achieve partial hydrogenation of the substrates using PtO_2 and either HCl or $\text{CF}_3\text{CO}_2\text{H}$, or mixture of the two. Depending on the conditions applied and the substrate employed different products are derived. Quinolyl and pyridyl compounds (2-substituted with a carbonyl group) provide clean and total formation of the desired amino alcohol with the catalytic system $\text{PtO}_2/0.5$ equiv. HCl. All other hydrogenation conditions lead to complex mixtures of products. When the heterocyclic ring is substituted by an alkyl group, then only the system $\text{PtO}_2/\text{CF}_3\text{CO}_2\text{H}$ affords a single clean product with the complete hydrogenation of the aromatic ring. [43]

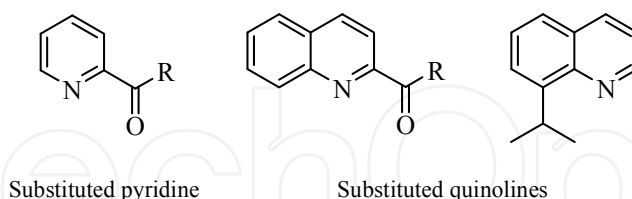
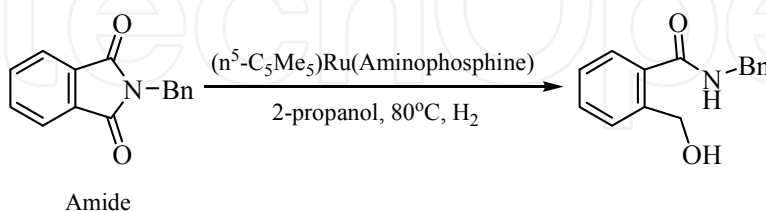


Figure 6. Substituted pyridine and quinolines as substrates for catalytic hydrogenation.

It is, therefore, clear that choosing the right conditions' combination for a given substrate is very important for achieving the hydrogenation, on the one hand, and for eliminating all byproducts and deriving a single pure product, on the other hand.

Amides constitute a very interesting moiety of heterocyclic compounds. The hydrogenation of the carbonyl of the heterocyclic ring can lead to important precursors for the synthesis of biologically active compounds. A very interesting point is that the carbonyl hydrogenation leads to a simultaneous ring opening. Ito et al. have successfully hydrogenated enantioselectively various amides and prochiral glutarimides as the first stage of a synthetic

process for the production of (-)-Paroxetine, an antidepressant. The hydrogenation requires high temperatures (80°C) and proceeds smoothly in relatively low H₂ pressure, in the presence of (η^5 -C₅Me₅)Ru(Aminophosphine), 2-propanol and *t*-BuOK. The reaction is presented in Scheme 12. Here, it is important to note the functionality of 2-propanol in the hydrogenation mechanism. Ito et al. suggest that 2-propanol mainly promotes the reaction by participating in the heterolytic cleavage of H₂ possibly through a hydrogen-bonding network and it hardly serves as a hydrogen source in the present reaction conditions. [44]



Scheme 12. Catalytic hydrogenation of amides by homogeneous Ru catalysts.

5. Selectivity in the hydrogenation reactions

We have already encountered the selectivity problem in almost every aspect of the catalytic hydrogenation. Indeed, it is such an important feature of the catalyst and the reaction conditions that cannot be ignored. It defines the refined hydrogenation method that focuses in a particular unsaturated center and which delivers a clean and high quality result. Additionally, we can refer to a few more examples. A very elegant work in the area of hydrogenation selectivity was made by Á. Molnár et al. [45] Covering the catalytic action of heterogeneous palladium catalysts, this could also be viewed under the scope of heterogeneous catalysis. Palladium is recognized as the best metal to achieve high regioselectivity with respect to the hydrogenation of dienes. Also, it exhibits high chemoselectivity in semihydrogenations. Considering conjugated dienes, the main selectivity principle is the same as in all multiple-bond compounds; the terminal double bond presents higher activity and is hydrogenated preferentially. After a monoene is formed, there is competition between the unreacted diene and the formed monoene. As a general principle, conjugated dienes are more reactive than non-conjugated dienes and monoenes. This is attributed to the fact that the entire π -system of dienes is involved in adsorption through di- π -coordination, which is more favorable than the d- σ mode of adsorption of a single double bond. Versatility in the hydrogenation of dienes is achieved via various supports for Pd: Pd-on-Al₂O₃, Pd-on-SiO₂, Pd-on-C, Pd-on-graphite, bimetallic Pd samples and so on. Investigation of the hydrogenation of butadiene and isoprene reveals a hydrogenation mechanism that involves 1,4 addition via π -allyl intermediates. Palladium favors the formation of 1-butene and *trans*-2-butene, in contrast to other metals such as gold and copper. The Pd particles dispersion has a maximum of activity at about 25-30%, and then the activity decreases with increasing dispersion. Carbon deposits partially poison the catalyst, allowing for the adsorption of butadiene that selectively leads to the formation of *n*-butenes. Pd-Cu-on-Al₂O₃ hydrogenates butadiene at 99% selectively to butenes, and the system Pd-Au-on-SiO₂ retains this selectivity. In the case of 1,5-hexadiene, a non-conjugated

diene, the high activity of Pd induces a double bond migration to form 2,4-hexadiene which then is reduced to 2-hexenes. Improvement of the selectivity of Pd towards *n*-hexenes is achieved by employment of TiO₂ support. Bimetallic catalysts show the same selectivity in 1,5-hexadiene, as in butadiene. An important application, catalytic hydrogenation of *trans,trans*-2,4-hexadienic acid using Pd-on-C leads selectively to the formation of semihydrogenated methyl *trans*-2-hexenoate, which is the desired product. The conclusions above are visualized in Table 1.

Another confirmation about the Pd selectivity for the hydrogenation of olefin double bonds in conjugated carbonyl systems is presented by B. C. Ranu and A Sarkar. [46] Using the catalytic system ammonium formate/Pd-C they successfully hydrogenated the olefin double bond that is conjugated to a carbonyl group, for a variety of substrates, without affecting the isolated double bonds. High efficiencies and short reaction times are the main characteristics of the method.

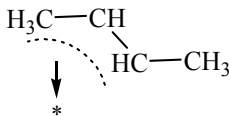
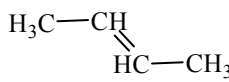
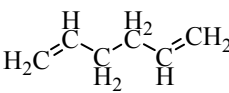
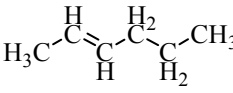
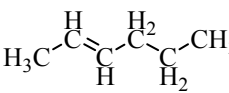
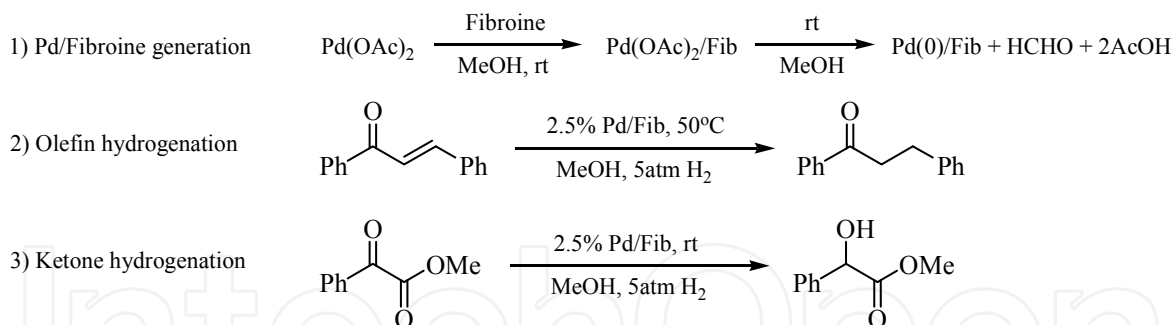
Catalysts	Substrates	Hydrogenation intermediates	Hydrogenation products
Pd-on-Al ₂ O ₃ Pd-on-SiO ₂ Pd-on-C Pd-on-graphite Pd-Ag-on- α -Al ₂ O ₃	$\text{H}_2\text{C}=\text{C}(\text{H})-\text{C}(\text{H})=\text{CH}_2$ Butadiene	 π -Allyl intermediate	$\text{H}_2\text{C}=\text{C}(\text{H})-\text{CH}_2-\text{CH}_3$ 1-Butene  <i>Trans</i> -2-butene
Pd-Cu-on-Al ₂ O ₃ Pd-Au-on-Al ₂ O ₃ Pd-Ag-on-SiO ₂ Pd-on-TiO ₂	 1,5-Hexadiene	 2,4-Hexadiene	 2-Hexene

Table 1. Supported Pd heterogeneous catalysis summary.

Fibroin-palladium catalyses the hydrogenation of olefinic double bonds, conjugated to aromatic ketones (Scheme 13). The ketone double bond remains intact. This, however, is not the case when there is an ester group in α position to the ketone. In both cases atmospheric conditions were employed and MeOH was the solvent of choice. A very important observation is that when MeOH is employed as solvent for the hydrogenation of benzyl ester derivatives, a partial hydrogenolysis of the substrate occurs. This can be avoided if THF replaces MeOH as the reaction solvent. [47]

Heterogeneous or immobilized homogeneous catalysts are the systems of choice in order to achieve selective hydrogenation with high purity products. Sahoo et al. employed an immobilized Ru triphenylphosphine complex over mesoporous silica SBA-15 and successfully hydrogenated, chemoselectively, prochiral and α,β -unsaturated ketones. [48] The turnover frequencies are very high and the enantioselectivity achieved for the prochiral ketones is also at very good levels. The chemoselectivities in the conversion of α,β -unsaturated ketones to the respective allyl alcohols are greater than 90%.



Scheme 13. Fibroin-palladium hydrogenation of olefinic and carbonylic confugated double bonds.

A Cp^*Ir (pentamethylcyclopentadienyl) complex is employed for the regio- and chemoselective transfer hydrogenation of quinolines. The reaction solvent also serves as the hydrogen source and in this case is 2-propanol. The quinolines bearing an electron donating or withdrawing group are readily hydrogenated, but for isoquinolines or pyridines this methodology is unsuccessful. The proposed mechanism involves the protonation of the quinoline and the simultaneous formation of an iridium-hydride, which is followed by the adsorption of the carbon-carbon double bond on the iridium-hydride complex. The final stage is a protonolysis to afford 1,2,3,4-tetrahydroquinoline. [49]

6. The case of 3,5-bisarylidene tetramic acids

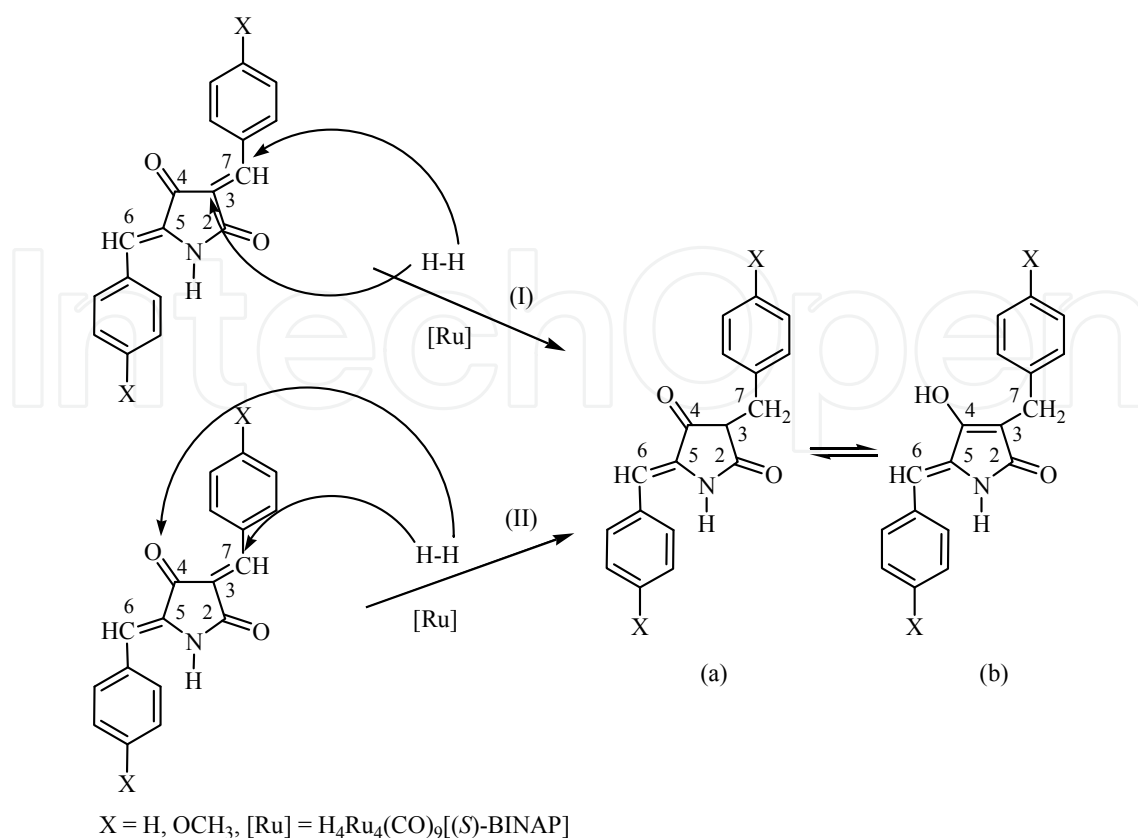
6.1. Chemoselective hydrogenation of C3=C7 double bond

The various oxidation states of Ru along with the tremendously rich list of available ligands for homogeneous Ru complex formation provide a strong background for the creation of specific catalysts to perform a certain function. An appropriately structured Ru complex can catalyze very difficult and hard to achieve transformations. [13]

The possibilities provided by the $\text{H}_4\text{Ru}_4(\text{CO})_9[(S)\text{-BINAP}]$ complex employed here, have not yet been sufficiently investigated. Since the purpose of application is the hydrogenation of 3,5-bisarylidene tetramic acids the conditions of the reaction must be controlled absolutely in order to avoid side reactions. Also, the purity of raw materials must be high, since a small impurity could initiate various uncontrolled and unidentified side reactions.

Judging from the cases we have encountered so far, there are two possibilities arising: A C3=C7 monoene selective hydrogenation, or a C7-C4=O 1,4-hydrogen addition (Scheme 14). To analyze this, first we have to outline the parameters affecting the mechanism, provided the catalyst is the $\text{H}_4\text{Ru}_4(\text{CO})_9[(S)\text{-BINAP}]$ complex:

- Reaction temperature.
- Gas H_2 reaction pressure.
- Reaction solvent.
- Substrate.



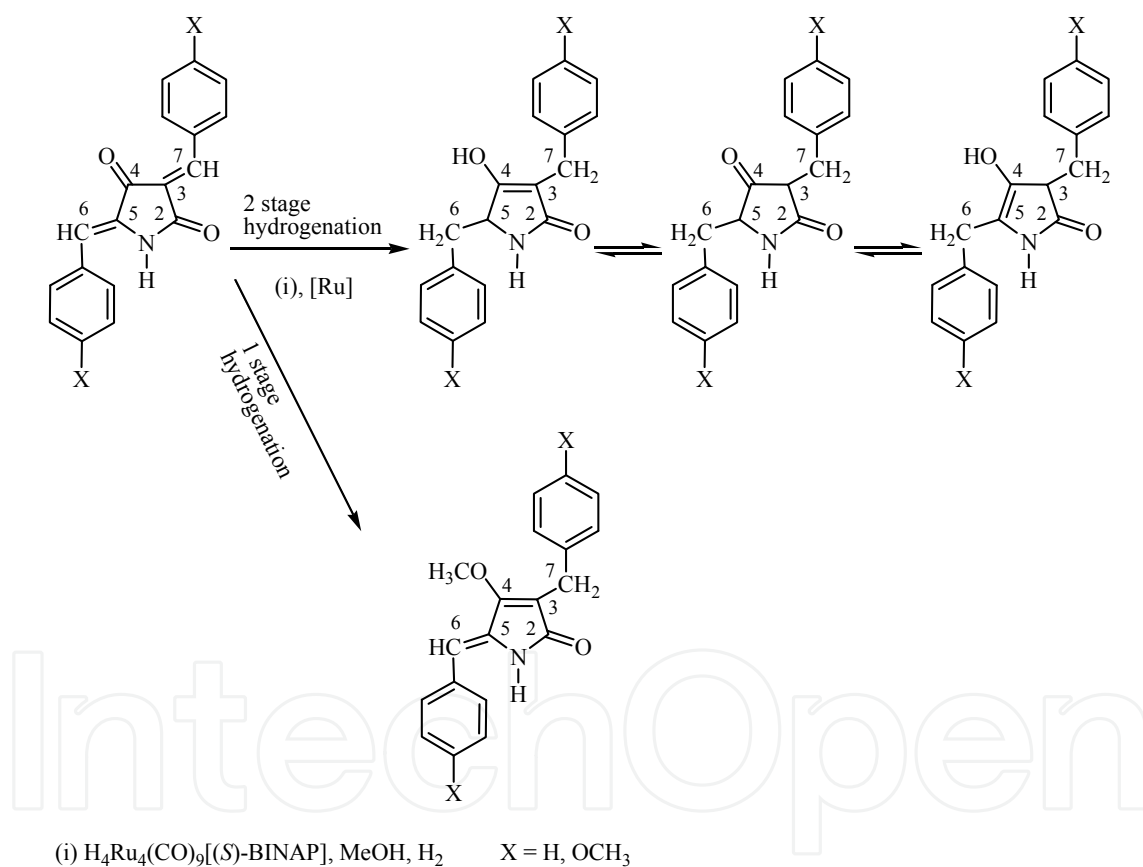
Scheme 14. Selective homogeneous catalytic hydrogenation of 3,5-arylidene tetramic acid, at C3-C7.

The -OCH₃ substituted aromatic groups afford slightly higher yields than the benzylidene derivatives. This means that the electron donating group of -OCH₃ enhances the catalytic hydrogenation. Additionally, the employment of EtOH as the reaction solvent leads to a selective hydrogenation at C3-C7, regardless the temperature and pressure applied. The later two parameters affect only the kinetics of the reaction at this point. However, if the reaction solvent is selected to be MeOH, the selectivity is much lower and the temperature defines the chemoselectivity of the reaction, as we will see further in the analysis. The exact mechanism of the hydrogenation depicted in Scheme 14, cannot be revealed (path I or path II) by this first stage hydrogenation, because of the keto-enol tautomerism observed by the ¹H NMR spectrum. [16] The dominant form is that of structure (b).

6.2. Second stage hydrogenation of the C5=C6 double bond

To better understand the mechanism we need to examine the results of the second stage of the hydrogenation process. Application of MeOH as solvent, a temperature as high as 80°C and hydrogen pressure at 60bar affords the highest yield of the C3-C7 and C5-C6 bi-hydrogenation (Scheme 15). As we observe in Scheme 15 there is still an extended keto-enol tautomerism, observed once again in the ¹H NMR spectrum, which does not allow for an enantioselective hydrogenation. The most important observation, however, is that the 4-methoxy compound, formed with a 24% yield approximately, does not proceed to a second stage hydrogenation as the 4-hydroxy compound does.

From this we derive that after the first stage hydrogenation there is a competitive methylation of the 4-hydroxy group. The catalyst/MeOH combination provides the necessary acidity for this reaction to proceed. The most important observation, however, is that the second stage hydrogen addition does not proceed in the case of the 4-methoxy derivative. This can be attributed to steric effects that inhibit the Ru-substrate bonding. Also, there is no possibility to the formation of the 4-ketone tautomer. This indicates that the C5-C6 hydrogenation proceeds with a 1,4-addition. The Ru catalyst attaches to the C4=O carbonyl and the C6 carbon of the 1st stage hydrogenated product (a) of Scheme 14. That very same mechanism could also be the case for the 1st stage hydrogenation depicted in Scheme 14, path (II). This mechanism is very close to the one reported by Chandiran et al., presented in Scheme 2. [18] The difference in the case of the $\text{H}_4\text{Ru}_4(\text{CO})_9[(S)\text{-BINAP}]$ complex is that the metal hydrides are already formed, on four separate nuclei, increasing the activity of the catalyst.



Scheme 15. Second stage hydrogenation of 3,5-bisarylidene tetramic acids and keto-enol tautomerism of the bi-hydrogenated product.

Returning to the original hypothesis of the α,β -unsaturated ketone-blocks existing in the heterocyclic ring we can conclude the following:

- There is no chemoselective hydrogenation of the aromatic olefins, but rather a hydrogenation of the α,β -unsaturated ketone to a saturated ketone. The enolic form appears later, as a keto-enol tautomerism.

- The hydrogenation does not occur as a 1,2-addition but rather as a 1,4-addition involving the complexation of a Ru nucleus to the C4 carbonyl group.
- The C4=O-C3=C7 unsaturated structure is more activated than the other unsaturated groups within the molecular structure of the substrate.
- The C2=O-C3=C7 unsaturated ketone is not active under the particular reaction conditions, probably because of the electron withdrawing nitrogen atom.

The above clues illustrate a direct relationship between the electron density of the conjugated double bonds and the antagonistic activity of the separate unsaturated centers coexisting in the substrate structure.

6.3. Proposed mechanism for the hydrogenation of 3,5-bisarylidene tetramic acids

Clapham et al. have extensively investigated the mechanisms of the hydrogenation of polar bonds catalyzed by Ruthenium hydride complexes. [50] We will focus in the case of hydrogenation via hydrogen gas, and not transfer hydrogenation, of carbonyl compounds. The reaction types are divided in: Inner sphere hydrogenation and outer sphere hydrogenation (Figures 7 and 8). One deficiency of the catalysts that operate by inner sphere hydride transfer is that they are often not very selective for C=O bonds over C=C bonds in, for example, the reduction of α,β -unsaturated ketones and aldehydes. The outer sphere mechanism occurs when the C=O bond has a low hydride affinity so that electrophilic activation is required either by an external electrophile or an internal electrophile attached to an ancillary ligand. When the ancillary ligand provides a proton to the ligand, during the hydride transfer, then the mechanism is characterized as “metal-ligand bifunctional catalysis”. It is discovered that complex hydrides of the type $\text{Ru}(\text{H})_2\text{H}_2(\text{PPh}_3)_3$ react readily with ketones at low temperatures (20°C), in contrast to the CO and Cl substituted Ru complexes, such as $\text{Ru}(\text{H})(\text{Cl})(\text{CO})(\text{PPh}_3)_3$ that react with ketones only at high temperatures (approximately 100°C) because of the electron withdrawing groups CO and Cl.

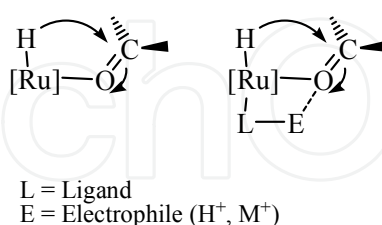


Figure 7. Inner sphere hydrogenation mechanism.

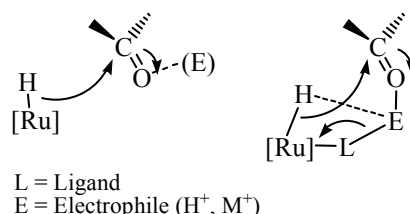
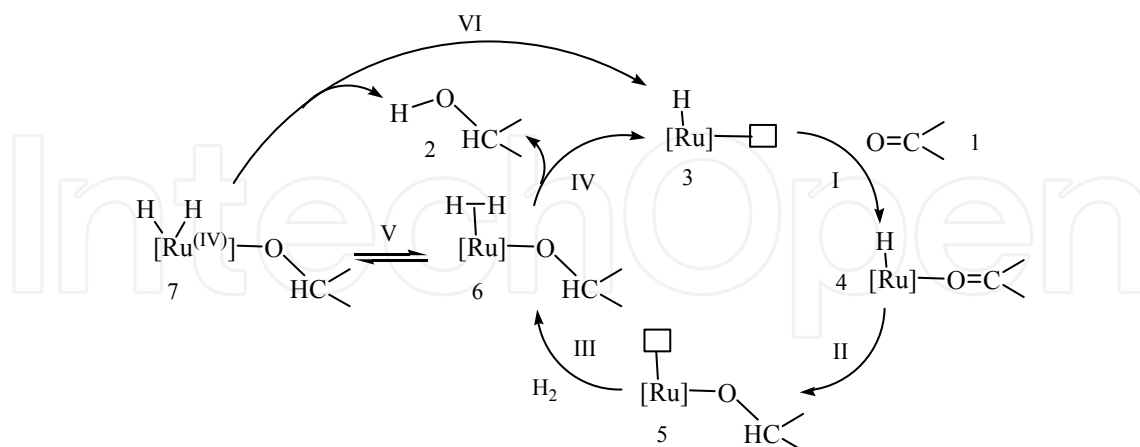


Figure 8. Outer sphere hydrogenation mechanism.

The generalized catalytic cycle for the inner sphere hydrogenation mechanism of C=O bonds is depicted in Scheme 16.

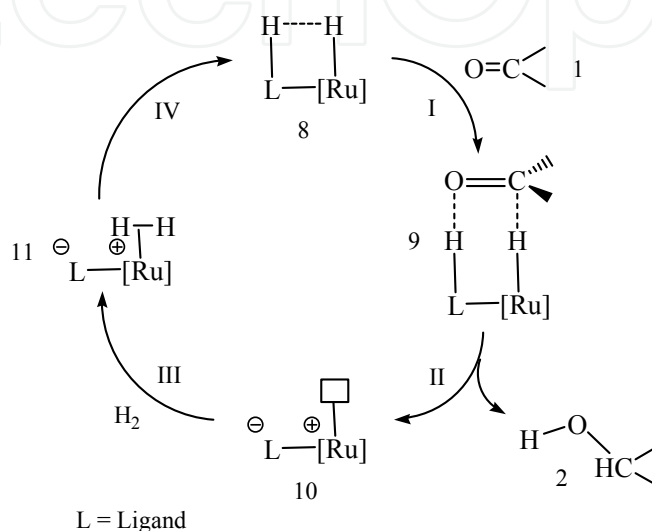


Scheme 16. Generalized catalytic cycle for the inner sphere hydrogenation of C=O bonds.

The cycle starts with the addition of the substrate (1) to the coordinatively unsaturated Ru(II) hydride species (3) giving the complex (4) (step I). The hydride species (3) is usually formed from a catalyst precursor at the very beginning of the catalytic reaction and is not isolated itself (see below). A hydride migration (step II) affords the new unsaturated ruthenium species (5) to which dihydrogen coordinates (step III) affording the dihydrogen species (6). A substrate insertion (step I) and a hydride migration (step II) are usually very fast so only the product (7) can be observed. Complex (6) can further react in two ways: Protonation of the coordinated substrate affords the product (2) releasing the regenerated catalyst (3) (step IV) or the coordinated dihydrogen can oxidatively add to the Ru(II) center giving a dihydride ruthenium(IV) species (7) (step V), followed by elimination of the product (2) and regeneration of the active catalyst (3). It should be noted that it is often impossible to experimentally distinguish between path IV and path V \rightarrow VI. Catalytic reactions for which the inner sphere hydrogenation mechanism has been proposed have several features in common, regardless of the solvent used (organic, water or biphasic system). They all require relatively high temperatures (50–100°C, in some instances even higher) and high dihydrogen pressures (around 50 atm). The catalyst-to-substrate ratio is usually small and no additives are necessary for the reaction to proceed. Step III in the Scheme 16 is generally recognized as the turn-over-limiting step.

A non-classical outer sphere mechanism, for the hydrogenation of polar multiple bonds, is shown in Scheme 17. This mechanism involves a hydride on the ruthenium catalyst and a proton on one of the ancillary ligands in a position to form a hydridic–protonic interaction (structure 8). The substrate (1) coordinates in step I by forming an outer sphere interaction between the atoms of its polar multiple bond and the proton and hydride of the complex (9). This interaction allows for the simultaneous transfer of the hydride and the proton (step II) producing the hydrogenated substrate (2) and a ruthenium complex with a vacant coordination site, (10). This 16-electron ruthenium center is usually stabilized by π -donation from the deprotonated ligand into the empty d-orbital. Hydrogen gas can then coordinate at

this open site (III) producing a dihydrogen complex intermediate or transition state (11). The dihydrogen ligand heterolytically cleaves in step IV to re-form the original hydride complex 10. This exact type of mechanism is suggested by Chaplin and Dyson for the Bis-phosphine Ruthenium(II)-Arene chemoselective catalytic hydrogenation of aldehydes, in the presence of olefinic bonds. In fact, the complex $[\text{RuCl}(\text{PPh}_3)(\text{P}(p\text{-tol})_3)(p\text{-cymene})]\text{PF}_6$ affords a 82% selectivity for the hydrogenation of the C=O double bond of a 1:1 styrene/benzaldehyde mixture, while when we add 5 equivalents of NEt_3 in the original reaction mixture the selectivity moves to 90% towards the hydrogenation of the olefinic bond C=C. [51]

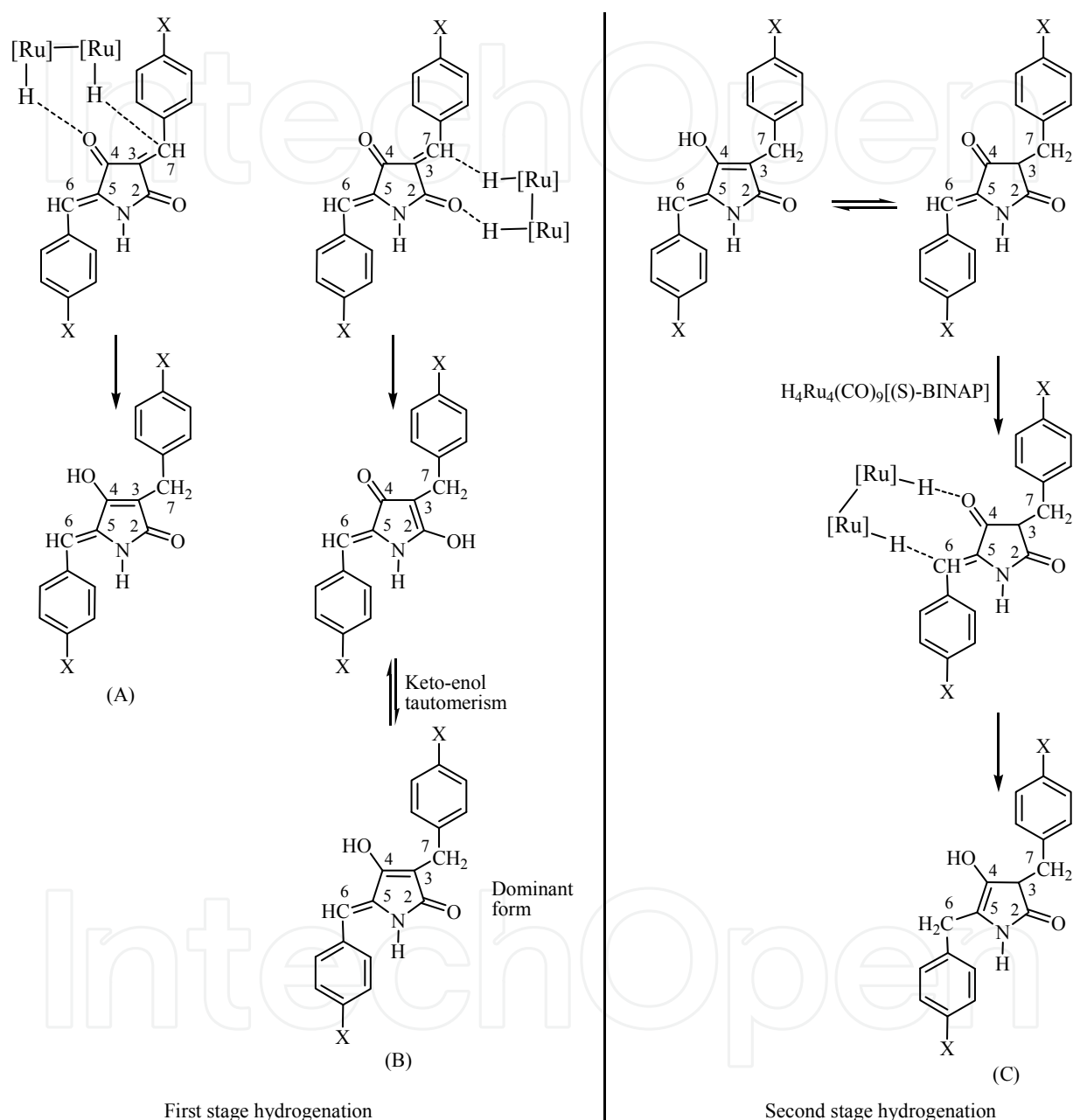


Scheme 17. Generalized catalytic cycle for the outer coordination sphere hydrogenation of the C=O bond catalyzed by ruthenium catalysts where the hydride addition to the substrate is assisted by an ancillary ligand.

The fact that the ruthenium complex $\text{H}_4\text{Ru}_4(\text{CO})_9[(S)\text{-BINAP}]$ used for the hydrogenation of 3,5-bisarylidene tetramic acids consists of four nuclei allows for a 1,4-interaction of the substrate with the catalyst, following a mechanism similar to that of the outer coordination sphere (Scheme 17). However, the presence of multiple Ru nuclei may prevent the ligands of the catalyst complex from playing a role to the direct interactions with the unsaturated sites: The Ru-H- group is evidently more functionalized, than the Ru-L-H- group, and will preferably bond at the unsaturated center. It is possible that this is the preferred mechanism for both hydrogenation stages. Scheme 18 depicts the possible catalyst-substrate interactions for the two hydrogenation stages according to the previous assumption.

The presence of the 4-ketone is essential for the complexation of the substrate on the catalyst. The first stage has two possibilities of complexation and as we will discuss later in the text the activation energy of the first stage hydrogenation is much lower than that of the second stage hydrogenation. In the case of path (B) it is discovered by ^1H NMR analysis that the 2-ketone-4-enol form is the dominant one. [16] This form, however, makes the second stage hydrogenation a more difficult to accomplish process. Since the presence of 4-ketone is required, and this form appears only in a small percentage compared to the 4-enol form, it is kinetically more difficult to achieve this second stage hydrogenation. So, longer reaction

times are required and higher temperature-pressure conditions. This mechanism also explains why the 4-methoxy derivative it is not hydrogenated on a second stage. Hydrogen-transfer mechanisms are not considered in the analysis, since the solvents employed (DCM, THF, EtOH, MeOH) are unlikely to be proton donors under the reaction conditions.



Scheme 18. Possible catalyst-substrate interactions for the $\text{H}_4\text{Ru}_4(\text{CO})_9[(\text{S})\text{-BINAP}]$ catalyzed two-stage hydrogenation of 3,5-bisarylidene tetramic acids.

Studies on the mechanism of hydrogenation of acrylamide using a Rh(I) complex performed by Verdolino et al. describe the behavior of the conjugated acrylamide system in hydrogenation conditions. [52] It is certain that the catalytic mechanism for Rh(I) is different than that of Ru(II). Still, the study reveals that the hydrogenation of acrylamide (Figure 9) is

directed to the olefinic double bond, while the carbonyl double bond remains intact. This is in accordance with the observation that the 2-ketone of the 3,5-bisarylidene tetramic acids is not activated by the hydrogenation conditions applied. This is also confirmed in the case of 3-ethoxy pyrrolidinone hydrogenation we have already mentioned. [15]

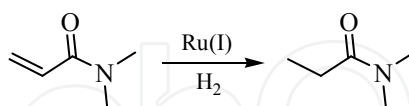


Figure 9. Ru(I) catalyzed hydrogenation of acrylamide.

6.4. Solvent, temperature and pressure effect on the Ru(II) catalyzed 3,5-bisarylidene tetramic acids' hydrogenation

The hydrogenation results for 3,5-bisarylidene tetramic acids depending on the reaction solvent applied are presented in Table 2. It is apparent that the mechanism for the hydrogenation of polar bonds is enabled in the presence of polar solvents. Employment of DCM as the sole reaction solvent does not afford any hydrogenated product. THF provides moderate results. With THF we can obtain good conversion for the first stage of the process, but results are very poor for the second stage. Ethanol gives very good results for the first stage hydrogenation, but fails to achieve second stage hydrogenation, even at elevated temperature and pressure. However, it serves as a tool for controlling the reaction outcome in terms of chemoselectivity. Ethanol is a safe chemical solvent, appropriate for green chemistry applications. For this reaction, it is the solvent of choice if the mono-hydrogenated product is the desired one. Methanol is the most polar amongst the solvents of this study. Methanol makes accessible the second stage hydrogenation, which indicates that stronger polarity conditions are required for the second stage hydrogenation. On the other hand, using methanol makes it more difficult to control the chemoselectivity of the reaction, and it will require a lower reaction temperature (60°C) to obtain a higher percentage of the mono-hydrogenated product (3 or 5). [16]

Entry	Substrate	S/C	Concentration	Solvent/DCM (v/v)	Temp (°C)	Press (bar)	Time (h)	Conversion	
			(M)					3	4
1	1	250	0.0018	MeOH (24:1)	100	60	20	4.7	94.2
2	1	500	0.0012	EtOH (24:1)	100	60	19	94.0	5.9
3	1	493	0.0034	THF (20:1)	100	60	20	94.4	5.5
								5	6
4	2	120	0.0010	MeOH (24:1)	100	60	20	24.8	73.9
5	2	405	0.0012	EtOH (24:1)	80	60	20	95.0	5.0
6	2	700	0.0020	THF (20:1)	100	60	20	25.4	8.9

S/C = Substrate/Catalyst molar ratio.

Table 2. Solvent effect on the Ru(II) catalyzed 3,5-bisarylidene tetramic acids' hydrogenation.

Numbering of the substrates and products of Table 2 is with respect to Figure 10.

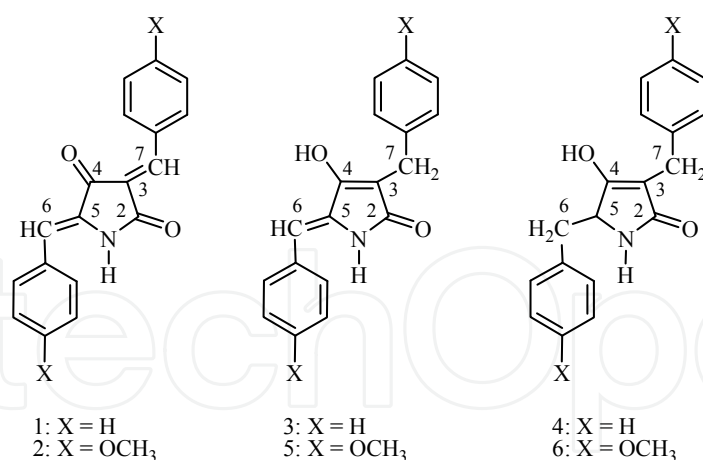


Figure 10. Substrates and products as they appear in Table 2.

A very interesting case of pronounced solvent effect is reported by Haddad et al. in the catalytic asymmetric hydrogenation of heterocyclic ketone-derived hydrazones. This study reveals an inversion in the enantioselectivity of the hydrogenation when the solvent of the reaction is changed from MeOH (85% e.e.) to DCE (-27% e.e.). Extensive study ruled out the hydrazone geometry or the hydrogenation via an endocyclic alkene as possible factors for the inversion of the configuration. This study also supports the fact that polar solvents as MeOH and EtOH afford higher selectivity values, whereas pentanol and DCM give moderate results. [53]

To return to the 3,5-bisarylidene tetramic acids hydrogenation, the applied temperature and pressure do affect the reaction outcome, but not as strongly as the solvent. [16] As we mentioned before, elevated temperature and pressure (above 80°C and 40bar respectively) is required for the ruthenium catalyst to achieve the hydrogenation of the substrate. In this case, mild hydrogenation conditions are not sufficient for a successful outcome of the process.

Mechanism decryption can be achieved, in most cases, by specially designed experiments and computational methods. Isotope kinetic studies and DFT computational methods promise to enlighten the catalytic mechanism of $H_4Ru_4(CO)_9[(S)\text{-BINAP}]$ catalyst for the hydrogenation of olefin and carbonyl double bonds. Future implementation of these methods will provide additional data to bring us one step closer to understanding the catalytic activity of this tetra-Ru-nuclei complex.

7. Heterogeneous versus homogeneous catalytic hydrogenation

We have already encountered many cases of heterogeneous and homogeneous catalytic hydrogenation reactions. Heterogeneous catalysts are commonly used in the form of powders for slurry and fluidized bed reactions or as formed bodies for fixed bed hydrogenations. The addition of promoters and adjustments in particle size and porosity allow for these catalysts to be fine tuned for specific reactions. Homogeneous catalysts are also very flexible where the selection of the transition metal, ligands and reaction conditions can lead to highly selective hydrogenations. The separation problems associated with homogeneous catalysts have led to the development of heterogenized homogeneous

catalysts via the fixation of the active complexes on organic or inorganic supports or via application in biphasic systems. While there has been some success in this area, there still remains a considerable amount of work to be done. [12]

At this point we can refer to a few more interesting heterogeneous catalytic reaction cases. The recent study presented by Bridier and Pérez-Ramírez demonstrates the possibility of selective catalytic hydrogenation of conjugated dienes and ene-yne. [54] Reactions are carried out in ambient conditions. Interesting observations arise from the results of valylene gas-phase hydrogenation to isoprene. Depending on the type of catalyst, Pd or Cu-Ni, and the H₂/Substrate ratio it is possible to selectively derive either isoprene or mono-olefins. At low ratios oligomers are formed at a high percentage, while in high ratios mixtures of isoprene and mono-olefins are derived. Since Pd highly favors the formation of active hydrogen species, it shows rather higher performance compared to the Cu-Ni system and modified Pd catalysts. However, very high H₂/Substrate ratios ultimately lead to cracking. Most of the catalysts employed favor the isomerization of the hydrogenated products leading to 1,4-hydrogen addition rather than 1,2-hydrogen addition. Cu is the only catalyst for which the isomerization is not observed.

A comparative study for the hydrogenation of binary activated ketones mixtures over modified and unmodified Pt/alumina heterogeneous catalyst sheds light on the mechanism of chiral and racemic hydrogenation of ketones. [55] Binary mixtures of ethyl pyruvate, methyl benzoylformate, ketopantolactone, pyruvic aldehyde dimethyl acetal and trifluoroacetophenone are subjected to hydrogenation in either toluene or acetic acid, on platinum/alumina unmodified catalyst (racemic hydrogenation) or modified with cinchonidine (chiral hydrogenation). The experimental conditions are those of the Orito reaction. Depending on the racemic/chiral condition a reverse is observed in the hydrogenation rate of the activated ketones. This verifies the adsorption model for the hydrogenation reaction that is proposed in the Orito reaction. The intermediate complexes are determined by the chiral modifier, the substrate and the reaction conditions. This indicates that still the heterogeneous catalytic processes need further clarification and more experimental data to describe the phenomena in more details.

8. Conclusion

The catalytic hydrogenation of olefinic and carbonylic double bonds depends on a number of parameters that shape the outcome of the reaction. During this analysis we encountered many examples where the careful choice of parameters and design of the hydrogenation process leads to the desired product, eliminating any byproducts. Summarizing the most important parameters we can generate the following list:

- Catalyst
- Substrate interactions
- Unsaturated center type
- Reaction solvent
- Reaction conditions

The substrate interactions and the nature of the unsaturated center constitute the first most important parameter. It defines the strategy for the successful hydrogenation. Interactions involve intramolecular electron effects, as a result of the presence of a heteroatom, a functional group or conjugated double bonds. Internal hydrogen bonds and large substitution groups define the activity and approachability of an unsaturated center. Intermolecular interactions mostly refer to the active sites of the substrate that may form stable bonds with the catalyst, the solvent or another functional moiety to the formation of an intermediate. Knowledge of the structure specificities can direct the entrepreneur to the right catalyst, solvent and conditions selection. Olefinic double bonds and especially conjugated C=C bonds, have proven to be very susceptible to hydrogenation, under various conditions, with high yield and good selectivity. On the other hand, carbonylic double bonds are harder to hydrogenate, and the breakthrough by Knowles and Noyori was the trigger for the successful design of novel versatile homogeneous catalysts which can hydrogenate C=O bonds under mild conditions.

Homogeneous catalysts of Rh, Ru and Ir afford the best results in terms of yield and selectivity. Given the fact that chiral ligands have a constantly increasing number, they provide us with more possibilities and now we are practically able to design a particular ligand for a particular hydrogenation. Heterogeneous modified Ni, Cu, Pt and Pd catalysts are most popular for industrial synthetic applications, because of their lower cost and the recovery option. They present good results for the hydrogenation of olefins and conjugated olefins, but give only moderate results for C=O hydrogenation.

The reaction solvent is the most important of the reaction parameters, as it can affect the yield, the selectivity and the overall outcome of the hydrogenation. Polar bonds, like C=O, usually demand the presence of a polar solvent (alcohol). Non polar solvents can be chosen for reasons of solubility, or when polar conditions can affect the substrate and the enantioselectivity of the product. In most cases, polar solvents give better results, but in order to avoid undesired hydrogenolysis or isomerization phenomena, a less polar solvent must be chosen (e.g. 2-propanol or THF). Employment of a Ru homogeneous catalyst usually demands the presence of a polar solvent that participates in the hydrogenation mechanism, enabling the intermediate hydride formation. Choosing the right Metal-Ligand combination minimizes the need for intense temperature and pressure hydrogenation conditions. There are applications, however, when elevated temperature (over 80°C) and pressure (over 50bar) is requested for the hydrogenation to succeed. Most studies indicate that higher selectivity is related to mild reaction conditions.

3,5-Arylidene tetramic acids are catalytically hydrogenated in two consecutive stages, by the $\text{H}_4\text{Ru}_4(\text{CO})_9[(S)\text{-BINAP}]$ complex. This substrate consists of an extended conjugated system based on the heterocyclic lactame nucleus. The four-Ru-nuclei complex is able to form direct hydride bonds to the C=O and C=C unsaturated centers and a 1,4-hydrogenation mechanism is proposed. This process delivers high yield and chemoselectivity in polar solvents and it can be controlled by choosing the alcohol solvent (MeOH or EtOH) and the reaction temperature. The hydrogenation of heterocyclic compounds has not yet been fully charted. A complex structure like that of an unsaturated, heterocyclic compound needs to be carefully manipulated to avoid side reactions during the hydrogenation process.

Innovation in the field of pharmaceuticals and fine chemicals drives the research of catalytic complexes and organic substrates in new fascinating areas and the future is very promising for the development of chemical catalysts that will function in a protein-like manner for the highly selective hydrogenation of unsaturated centers, leaving the rest of the substrate structure intact and with a high atom economy. Modern isotope kinetic studies and DFT theoretical calculations are tools in the service of catalyst and process design for optimizing the hydrogenation results and could be cooperatively employed to afford maximum results.

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