Current Topics in Catalysis
Vol. 10, 2012

Review

Metal-catalyzed isomerization of allylic and propargylic alcohols in aqueous media

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ABSTRACT

Metal-catalysis in aqueous medium has led in recent years to the development of a huge number of new and greener synthetic methodologies in organic chemistry. Also, the search for organic reactions that proceed with efficiency, selectivity and atom economy has emerged as a prime goal in synthetic chemistry. Among the organic processes that take place with atom economy, isomerization reactions are typical examples because no by-products are generated. In this regard, the isomerizations of readily accessible allylic and propargylic alcohols, mainly giving carbonyl compounds, provide a simple synthetic route to these very valuable raw materials in organic chemistry. In this review, an overview of the progress achieved on the catalytic isomerization of allylic and propargylic alcohols in environment-friendly aqueous media will be presented.

KEYWORDS: isomerization processes, allylic alcohols, propargylic alcohols, aqueous media, metal-catalysis

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1. INTRODUCTION

With most of the chemical transformations taking place in solution, the role of solvents in chemistry is of paramount importance. Although, in principle, any liquid may be used, organic solvents have been traditionally employed for both synthetic chemistry and extraction procedures, often creating a great deal of safety, health and environmental issues due to their flammability, toxicity and volatility. The ever-growing need to develop synthetic protocols fulfilling the sustainability's criteria, in response to social pressure, has triggered intensive endeavors focused on the search of alternative

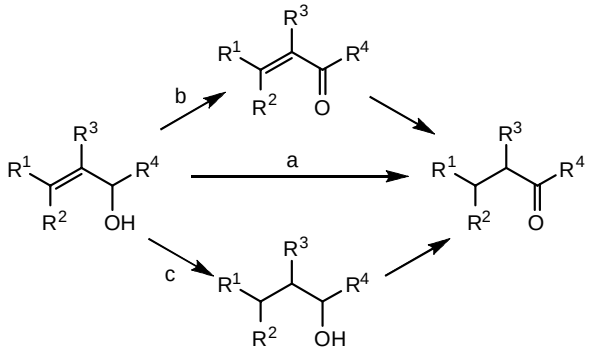
reaction media based on less damaging solvents [1, 2]. In this sense, water is undoubtedly one of the greener solvents one can imagine in terms of availability, safety and environmental impact. Thus, it is not surprising that in the last two decades, the aqueous metal-catalysis has emerged as an attractive approach for organic synthesis, a huge number of water-soluble catalysts being devised to promote such processes [2].

The efficient use of raw materials also represents an important factor to minimize environmental impact, reducing waste generation. Hence, the complete control of chemo-, regio- or stereo-selectivity is primordial to achieve greener synthetic protocols. On the other hand, the development of processes with high atom economy is a key factor to decrease waste production [3]. Among the organic reactions that proceed with high atom economy, isomerization processes are typical examples because all the atoms of the initial substrate end up in the final product. In this regard, the isomerizations of readily accessible allylic and propargylic alcohols, mainly leading to carbonyl compounds, provide a simple and attractive synthetic route to these very valuable raw materials in organic chemistry [4]. Most of these processes have been performed in organic solvents [5-7], however, recent efforts have been made to develop efficient catalytic systems capable of promoting these transformations in aqueous media [6]. The aim of this contribution, which covers the literature published up to December 2011, is to provide a detailed overview on the developments achieved in this field.

2. Redox isomerization of allylic alcohols

2.1. State of the art in organic media

The redox isomerization of allylic alcohols catalyzed by transition-metal complexes is a useful and straightforward synthetic route to carbonyl compounds (Scheme 1, path a) which conveniently replaces the classical two-step sequential oxidation/reduction reactions (Scheme 1, path b or c). Besides step economy, one advantage of redox isomerization is to avoid the use of toxic and/or expensive oxidation and reduction reagents. Hence, during the last three decades, considerable efforts have been devoted to developing efficient



Scheme 1. The redox isomerization of allylic alcohols.

catalytic systems for this process [5, 6]. The transformation is based on the well-known ability of transition-metal complexes to assist the migration of carbon-carbon double bonds, that is, the catalyst turns the allylic alcohol into an enol which readily tautomerizes, generating the corresponding carbonyl compound [8].

Since the pioneering works reported in the 1960's [9], a wide range of transition-metal catalysts have been devised, the best performances being achieved with iron, ruthenium, rhodium, and, more recently, iridium based-complexes [5, 6, 10]. These redox isomerization processes, initially limited to simple allylic alcohols, have proven to be tolerant with a huge number of functional groups such as alcohol, ether, ester, ketone, amide, nitrile, nitro, halide and O-, N- or S-based heterocycles [8a, 11, 12]. The major restriction lies in the isomerization of allylic alcohols which present a C=C bond conjugated with an alkenyl or alkynyl function, and so, as far as we know, the transformation of 2,4-dien-1-ols and 2-en-4-yn-1-ols into the corresponding *γ*-enones and *γ*-ynones remains undone [11b, c]. Remarkably, substrates' reactivity strongly depends on the substitution pattern of the C=C bond. Thus, mono-substituted allylic alcohols (*i.e.* $R^1 = R^2 = R^3 = H$, in Scheme 1) give rise to the highest catalytic activities. In contrast, conversions of di- and tri-substituted substrates are, by far, more difficult and, as a matter of fact, only few catalytic systems could transform tri-substituted allylic alcohols under smooth conditions [10b, e, 12, 13]. Finally, it is worthy of note that, up-to-day, only one example of isomerization of a tetra-substituted substrate

(*i.e.* R^1, R^2 and $R^3 \neq H$, in Scheme 1) has been reported [13b].

With the availability of highly efficient catalysts, the redox isomerization processes are now applicable to structurally elaborated substrates, allowing their use in multi-step synthesis of high value added compounds. In this context, we must highlight the preparations of the naturally occurring pheromones muscone [12] and (+)-iso-exo-brevicomin [14], the marine alkaloid (-)-brevisamide [15], the fragrance Florhydral® [16] and the antitumor agent (-)-FR182877 [17], all of them including a redox isomerization step. On the other hand, remarkable results have been recently obtained in the development of asymmetric versions of this reaction, excellent enantiomeric excesses being achieved in some cases [12, 13c, 18].

2.2. Redox isomerization in aqueous media

2.2.1. Ruthenium catalysts

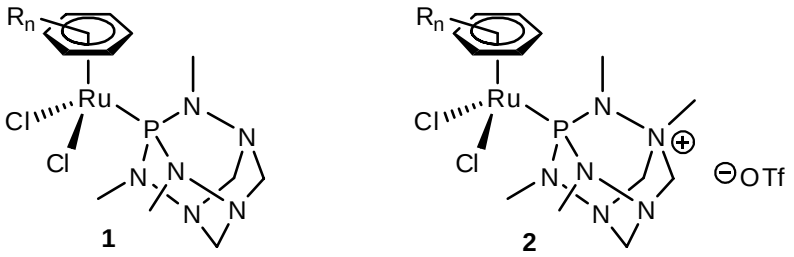
Undoubtedly, among all the metal-complexes used as catalysts in aqueous media, the most widely employed are those involving ruthenium. Oxidation numbers +II and +IV clearly predominate, with ruthenium(III) species being, by far, less common.

2.2.1.1. Ruthenium(II) precursors

The first ruthenium(II) catalyst used in water, namely $[Ru(H_2O)_6][OTs]_2$ (OTs = *p*-toluene sulfonate), was reported by Grubbs and co-workers in the early 1990's [8b,19]. High loading (10 mol%) of this hexaaqua-complex allowed the isomerization of mono-substituted allylic alcohols into the corresponding ketone or aldehyde under smooth conditions (45ºC). Unfortunately, oxidation by-products were also observed in some instances.

Since this seminal work, several ruthenium(II) catalysts have been developed, most of them being half-sandwich cyclopentadienyl- or arene-Ru(II) complexes. Their use enabled selective formation of the expected carbonyl compounds with lower metal loadings (*ca.* 1 mol%). However, they usually required higher reaction temperatures (*ca.* 80-100ºC) to be operative. In this context, Gimeno and co-workers prepared a series of water-soluble arene-Ru(II) derivatives containing hydrophilic phosphine ligands, including the tris(hydroxymethyl)phosphine complexes $[RuCl_2(\eta^6\text{-arene})\{P(CH_2OH)_3\}]$ and $[RuCl(\eta^6\text{-arene})\{P(CH_2OH)_3\}_2][Cl]$ (arene = C_6H_6, *p*-cymene, C_6Me_6) [20a], the phosphino-ammonium derivatives $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{PPh_{3-n}(OCH_2CH_2NMe_3)_n\}][SbF_6]_n$ (n = 1, 2, 3) [20b], and the cage-like phosphine precursors $[RuCl_2(\eta^6\text{-arene})(THPA)]$ (**1a-d**) [20c] and $[RuCl_2(\eta^6\text{-arene})(THPA\text{-}Me)][OTf]$ (**2a,b**; OTf = trifluoro methanesulfonate) [20c] (Figure 1). Good catalytic activities (TOF up to 1188 h^{-1}) were obtained with these complexes in the redox isomerization of mono-substituted allylic alcohols using water/*n*-heptane biphasic mixtures [20a] or pure water [20b, c] as reaction media. However, the efficiency dropped dramatically when di-substituted substrates were employed. For example, low TOF values (*ca.* 1 h^{-1}) were achieved in the isomerization of but-2-en-1-ol into butanal [20a].

Higher catalytic performances for these challenging substrates were reported by Crochet and co-workers



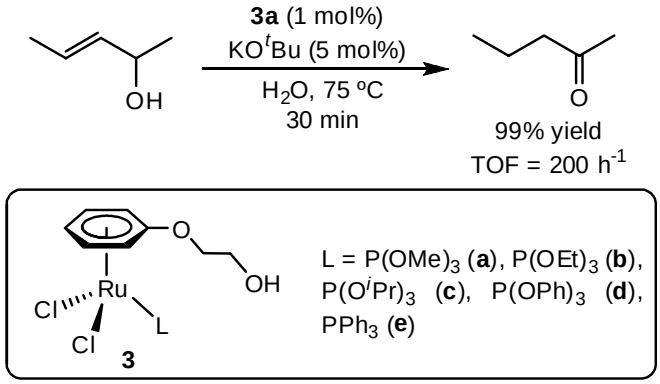
arene = C_6H_6 (**a**), *p*-cymene (**b**), 1,3,5-$C_6H_3Me_3$ (**c**), C_6Me_6 (**d**)

arene = C_6H_6 (**a**), *p*-cymene (**b**)

Figure 1. Some arene-ruthenium(II) catalysts with hydrophilic phosphine ligands.

using the highly water-soluble derivatives $[RuCl_2(\eta^6\text{-}C_6H_5OCH_2CH_2OH)(L)]$ (L = $P(OMe)_3$, $P(OEt)_3$, $P(O^iPr)_3$, $P(OPh)_3$, PPh_3) (**3a-e**) [21]. For instance, these catalytic systems were able to convert pent-3-en-2-ol into pentan-2-one in short reaction times, giving rise to TOF values up to 200 h^{-1} (a representative example is given in Scheme 2).

All the arene-ruthenium(II) precursors mentioned above required basic co-catalysts (KOH, KO^tBu or Cs_2CO_3) to reach high catalytic activities, moderate reaction rates being observed under neutral conditions [20b, c]. The role played by the base is the deprotonation of the hydroxyl group of the allylic alcohol thereby enhancing its coordinating ability [8]. A base-free catalytic system based on the arene-ruthenium(II) complex $[RuCl_2(\eta^6\text{-}p\text{-cymene})(L)]$ (L = 1-butyl-3-methyl imidazolin-2-ylidene) (**4**) (Figure 2), containing an *N*-heterocyclic carbene (NHC) ligand, has been developed by Joó and co-workers [22]. In this case, the reaction only proceeded in the presence of hydrogen (1 bar). Using this protocol, mono-substituted allylic alcohols led to the expected ketones, along with a small amount of the related saturated alcohols. Remarkably, the selectivity towards the ketones, optimum under neutral conditions, decreased upon addition of either acidic or basic buffer solutions. On the other hand, addition of a chloride source, *e.g.* NaCl, favored the isomerization over the hydrogenation allowing better selectivities. Both the base and the hydrogen gas could be avoided when the less sterically hindered NHC-derivative **5** and a higher reaction temperature (100ºC *vs.* 80ºC) were employed (Figure 2) [23]. Even better results were obtained with the water-soluble complexes **6a,b**, bearing κ^2-carbonate and sulfonated NHC ligands (Figure 2) [23]. Worthy of note, precursors **6a,b** presented unusual high efficiencies in the transformation of primary alcohols, such as prop-2-en-1-ol, into the corresponding aldehydes. As a general trend, ruthenium(II) catalysts are known to hardly isomerize such substrates [8a, 20a, 22, 24],



Scheme 2. Isomerization of pent-3-en-2-ol in water promoted by complex **3a**.

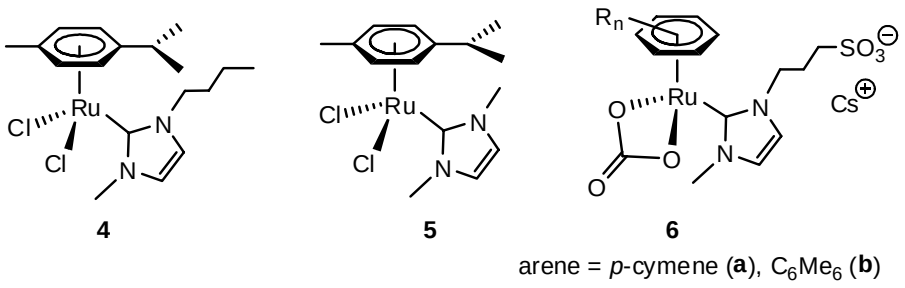


Figure 2. Arene-ruthenium(II) catalysts with NHC ligands.

presumably due to the progressive deactivation of the catalytic species through decarbonylation of the resulting aldehydes [25].

One of the major advantages of performing reactions in water is the possibility of separating easily the final product from the water-soluble catalyst by simple decantation of the biphasic medium or through liquid-liquid extraction. Active species could then be re-used in further catalytic cycles. In this context, several of the above-mentioned arene-ruthenium(II) catalysts have proven to be readily recyclable [20, 22, 23]. The best results were obtained with the phosphino-ammonium derivative $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(OCH_2CH_2NMe_3)_3\}][SbF_6]_3$ [20b], which could be used for at least 10 runs without significant loss of activity. With the same objective, a ruthenium-arene-PTA (RAPTA; PTA = 1,3,5-triaza-7-phosphatricyclo[3.3.1.1^{3,7}]decane) complex was grafted on the external layer of first, second and third generation phosphorus-containing dendrimers (**7** in Figure 3) [26]. These systems smoothly promoted the conversion of oct-1-en-3-ol into octan-3-one in a water/*n*-heptane biphasic mixture. Remarkably, a higher catalytic efficiency was achieved as the dendrimer generation increased, evidencing clearly a positive dendritic effect. The water-soluble first generation dendrimer could be recycled three times by decantation and removal of the organic phase. In a similar way, a RAPTA-type complex was also supported on the surface of silica-coated ferrite nanoparticles (**8** in Figure 3) [27]. The resulting heterogeneous catalyst **8** fully converted mono-, di- and tri-substituted allylic alcohols into the corresponding aldehydes or ketones. Moreover, this magnetic material was easily separated with the aid of an external magnet and reused in three further catalytic runs without notable decrease in its activity and selectivity.

As commented previously, the second main family of ruthenium(II) catalysts employed in the redox isomerization of allylic alcohols is constituted by cyclopentadienyl-derivatives. Within this series, the best performances were achieved with the water-soluble bis-phosphine complex $[RuCl(\eta^5\text{-Cp})(TPPMS)_2]$ (TPPMS = (3-sulfonatophenyl)diphenylphosphine sodium salt) under acidic conditions (buffered solutions), obtaining the highest conversions at pH 2 [25a]. This precursor, reported by Joó and co-workers, readily converted different mono-substituted allylic alcohols into ketones with excellent TOF values (up to 2226 h^{-1}). Interestingly, this catalyst usually employed at 60ºC, remained active even at room temperature, albeit slower reactions were observed in this case. Another striking feature is its high reactivity towards primary allylic alcohols enabling complete conversions into the corresponding aldehydes. A closely related CpRu(II) derivative, in which the chloride ligand was replaced by carbon monoxide, was also tested

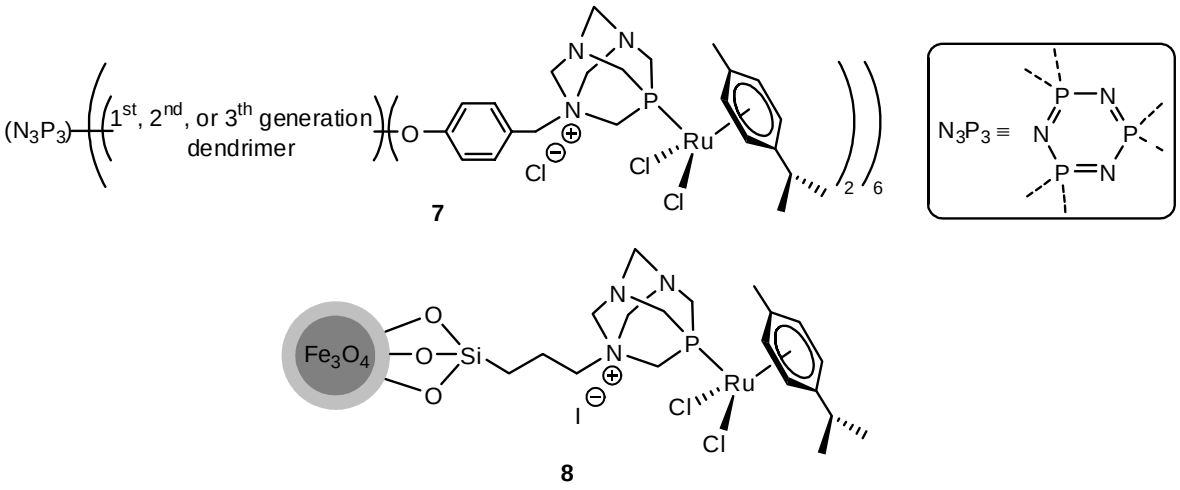
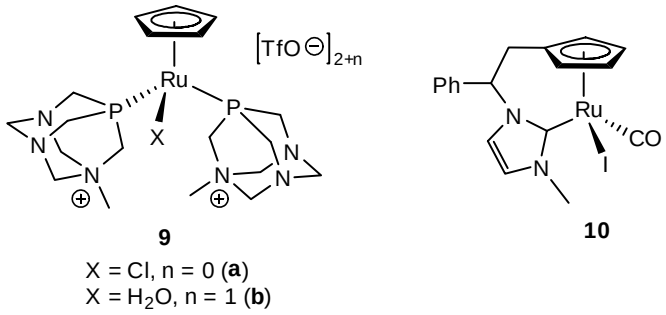


Figure 3. RAPTA complexes anchored to dendrimers **7** and nanoferrites **8**.

as catalyst with only little success [25a]. Similarly, other bis-phosphine cyclopentadienyl-complexes $[RuCl(\eta^5\text{-}Cp)(PTA\text{-}Me)_2][OTf]_2$ (**9a**) and $[Ru(\eta^5\text{-}Cp)(PTA\text{-}Me)_2(OH_2)][OTf]_3$ (**9b**, Figure 4) isomerized mono-substituted allylic substrates with low to moderate activities (TOF values from 6 to 162 h^{-1}) [28]. Once again, the reaction rates strongly depended on the pH medium, with the best results obtained under acidic conditions. This behavior has been ascribed to the interference between the phosphate anions of the buffer and the metal center at neutral or basic pH.

Redox isomerizations were also satisfactorily performed with the tethered cyclopentadienyl compound **10** associated with three equivalents of AgOTf (TOF values from 124 to 248 h^{-1}) [29]. However, this catalytic system is restricted to C=C mono-substituted substrates, low yields (< 20%) being achieved with the di-substituted ones.

More recently, the supramolecular catalyst **11**, generated by encapsulation of the $[Ru(\eta^5\text{-}Cp)(PMe_3)(NCMe)_2]^+$ cation in the host assembly $[M_4L_6]^{-12}$ (M = Al^{3+}, Fe^{3+}, Ga^{3+}, LH_4 = 1,5-bis(2,3-dihydroxybenzoylamino)-naphthalene), was studied by Raymond and co-workers (Scheme 3) [30]. Interestingly, through encapsulation, the stability of the organometallic complex in aqueous solutions considerably increased from few hours to several days. Furthermore, its water-solubility was also greatly improved, by at least one order of magnitude. Finally, the inclusion of the active species in the supramolecular guest allowed the modulation of its reactivity. As a matter of fact, both aliphatic and aromatic allylic alcohols (*e.g.* prop-2-en-1-ol, but-3-en-2-ol, 1-phenylprop-2-en-1-ol) could be converted by the free Cp-ruthenium(II) derivative, while only the aliphatic ones react with the supramolecular catalyst **11**;



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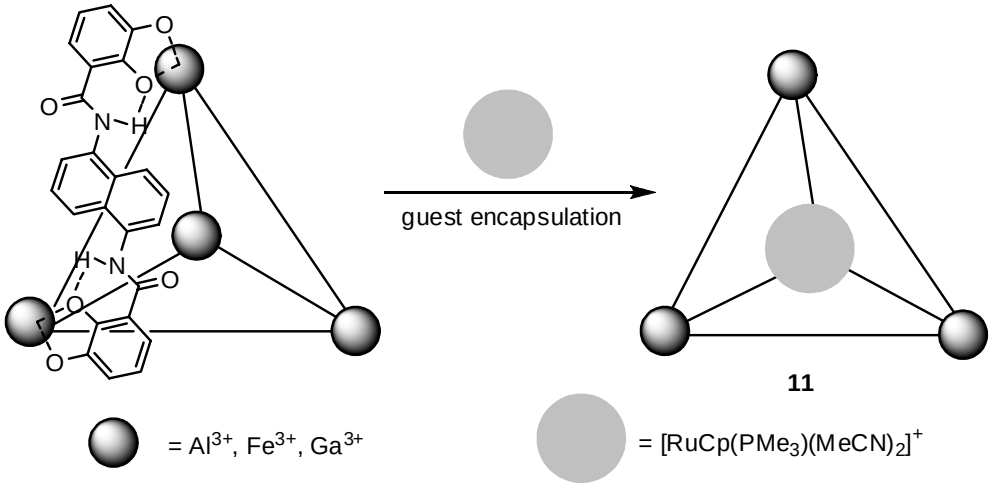
X = Cl, n = 0 (**a**)
X = H_2O, n = 1 (**b**)

10

Figure 4. Cyclopentadienyl-ruthenium(II) catalysts **9a-b** and **10**.



Scheme 3. Water-soluble host-guest systems for the redox isomerization of allylic alcohols.

that is, the most hindered substrates could not insert into the internal cavity and remained unaltered.

In addition to cyclopentadienyl- and arene-ruthenium(II) precursors, the moderately active dinuclear catalysts [{RuCl(μ-Cl)(TPPMS)$_2$}$_2$] and [{RuCl(μ-Cl)(C=C=CPh$_2$)(TPPMS)$_2$}$_2$] have also been reported [25a]. The octahedral derivative [Ru(H$_2$O)$_2$(bipy')$_2$][OTf]$_2$ (bipy' = 6,6'-dichloro-2,2'-bipyridine), extremely efficient in organic media, was also tested in water, albeit with disappointing results [31].

2.2.1.2. Ruthenium(III) precursors

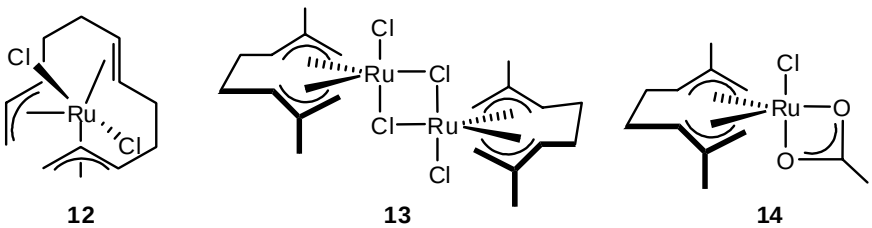
The μ^3-oxo-triruthenium cluster [Ru$_3$(μ^3-O)(OAc)$_6$(H$_2$O)$_3$][OAc], described by Blum and co-workers in 1979, was the first example of ruthenium(III) catalyst studied in aqueous media [9]. Its activity was strongly affected by the solubility of the substrates. Thus, allylic alcohols with long *n*-alkyl chains (*e.g.* dec-1-en-3-ol), which are poorly miscible with water, barely reacted even at 120ºC. This limitation could be overcome, to some extent, by adding a surfactant to the medium. Modest conversions were also obtained using the hydrated salt RuCl$_3$·xH$_2$O combined with TPPTS (TPPTS = tris(3-sulfonatophenyl) phosphine sodium salt) [18a]. Moreover, in this case, hydrogenated side products, due to a competing hydrogen transfer process, were generated along with the expected ketone.

Different Ru(III)-systems were also employed to promote the isomerization of but-3-en-2-ol into methyl-ethyl-ketone (MEK), an important industrial chemical, in monophasic water/diglyme mixtures. Moderate yields were achieved with RuCl$_3$·xH$_2$O, alone or associated with one equivalent of phenanthroline (phen) [32]. Somewhat better activity was obtained with the pre-formed phenanthroline complex [RuCl$_3$(dmso)(phen)] (dmso = dimethylsulfoxide), reaching a 88% yield of MEK after 6 hours of heating at 130ºC. Worthy of note, the ruthenium(II) analogue [RuCl$_2$(dmso)$_2$(phen)] proved to be less active. Finally, an almost complete transformation was attained using a RuCl$_3$·xH$_2$O/phen/HOTs catalytic system [33].

2.2.1.3. Ruthenium(IV) precursors

First examples of ruthenium(IV) catalysts only appeared very recently, but they provided excellent results in terms of scope, activities and selectivities. Thus, the bis-allyl-ruthenium(IV) precursors [RuCl$_2$(η^3:η^2:η^3-C$_{12}$H$_{18}$)] (C$_{12}$H$_{18}$ = dodeca-2,6,10-triene-1,12-diyl) (**12**, Figure 5) and [{RuCl(μ-Cl)(η^3:η^3-C$_{10}$H$_{16}$)}$_2$] (C$_{10}$H$_{16}$ = 2,7-dimethylocta-2,6-diene-1,8-diyl) (**13**) allowed high conversions of mono-, di- or tri-substituted allylic alcohols into the corresponding carbonyl compounds under neutral or basic conditions [8d, 34].

Remarkably, the high catalytic efficiency of complexes **12-13** is retained at very low metal loadings (10^{-4}-10^{-5} mol% of Ru), leading to impressive TON values of up to one million. The isomerization processes were found to take place faster in water than in THF (*e.g.* TOF = 2000 h^{-1} *vs.* 429 h^{-1} in the isomerization of oct-1-en-3-ol catalyzed by **12** in water and THF, respectively). This activity enhancement is probably due to the higher polarity of water which favors the chloride dissociation in the organometallic precursor as well as the deprotonation of the allylic alcohol to form the corresponding oxo-allyl anion [8]. Moreover, on the basis of theoretical calculations (DFT), direct participation of a coordinated molecule of water has been proposed, its main role being to promote the protonation of the metal-enolate fragment [8g]. Finally, we must



12 **13** **14**

Figure 5. Bis-allyl-ruthenium(IV) catalysts for redox isomerization reactions.

note that catalysts **12** and **13** could be recycled at least 4 consecutive times without notable decrease in activity after fractional distillation of the ketone generated. However, this procedure is limited to volatile products with boiling points below 100ºC. This restriction could be overcome by using the acetate derivative [RuCl(κ^2-OAc)(η^3:η^3-$C_{10}H_{16}$)] (**14**, Figure 5), which combines a high activity with a good solubility in water, enabling therefore, its recycling through liquid-liquid extraction [35].

Remarkably, the highly active catalysts **12** and **13** have found an industrial application in the large scale production of the analgesic drugs hydromorphone and hydrocodone. These relevant pharmaceutical compounds could be generated in aqueous media through the catalytic isomerization of the naturally occurring opiates morphine and codeine [36]. For example, using only 0.007 mol% of complex **13** (0.014 mol% of Ru), codeine was transformed into hydrocodone in good yield performing the reaction in a water/ethanol mixture (Scheme 4).

2.2.2. Rhodium catalysts

The carbonyl-rhodium(I) dimer [{Rh(μ-Cl)$(CO)_2$}$_2$] was the first example of a rhodium catalyst reported in aqueous medium [37]. Combined with a large excess of sodium hydroxide and a phase-transfer agent, it successfully converted different mono- and di-substituted allylic alcohols in a CH_2Cl_2/water mixture under very smooth conditions (25-30ºC). Surfactant proved to be essential to attain a good selectivity. A high effectiveness at low temperature (r.t.) was also observed with the catalytic system formed *in-situ* from [Rh(cod)$(NCMe)_2$][BF_4] (cod = 1,5-cyclooctadiene) and two equivalents of the water-soluble phosphine PTA [38]. Short reaction times (from 5 min to 3 h) were required to convert mono-substituted allylic alcohols in good yields. The catalytic system was also operative for more hindered substrates although longer times and higher temperatures were then needed.

Different *in-situ* generated or preformed rhodium(I) and rhodium(III) catalysts, containing phosphonated, carboxylated or sulfonated phosphines, have also been involved in redox isomerization processes, leading in general to modest conversions [39]. The best results were achieved with the zwitterionic rhodium(I) complex [Rh(sulphos)(cod)] **15** (Figure 6), in particular when secondary allylic alcohols were used [39d]. Lower activities were observed starting from primary allylic alcohols due to progressive decomposition of the catalytic species into the less active derivative [Rh(sulphos)$(CO)_2$], *via* decarbonylation of the resulting aldehydes.

Like the ruthenium cation [Ru(η^5-Cp)$(PMe_3)(NCMe)_2]^+$ described in section 2.2.1.1 (Scheme 3), the rhodium species $[Rh(PMe_3)_3(D_2O)_2]^+$ could be encapsulated into a supramolecular

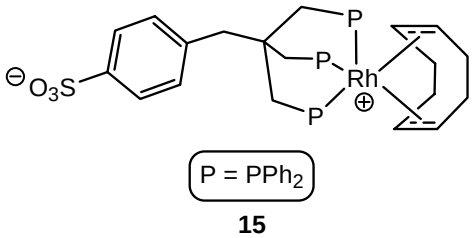


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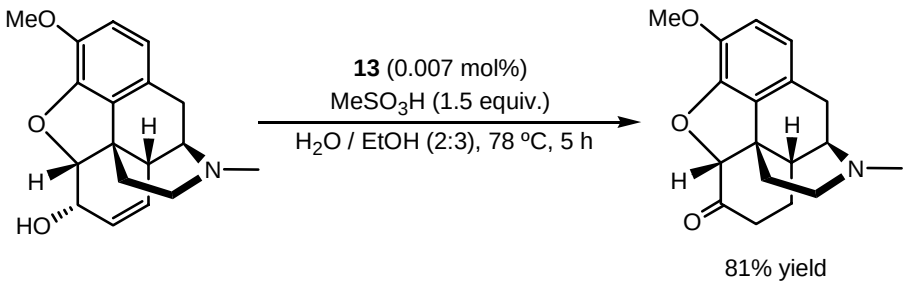
Figure 6. Structure of the zwitterionic rhodium(I) catalyst **15**.



Scheme 4. Catalytic isomerization of codeine into hydrocodone in aqueous medium.

$[Ga_4L_6]^{12-}$ (LH_4 = 1,5-bis(2,3-dihydroxybenzoyl amino)-naphthalene) tetrahedral assembly [40]. After initiation by treatment with H_2 (1 atm), this host-guest system was very active in the isomerization of allylic alcohols at room temperature. As observed for the ruthenium complex, the incorporation of the organometallic catalyst in the cavity resulted in highly specific size and shape substrate selectivities. Indeed, only allylic alcohols small enough to penetrate into the host assembly were converted into the corresponding carbonyl compounds.

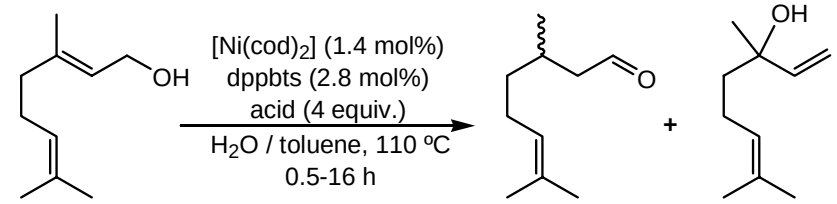
2.2.3. Other transition-metal catalysts

Although iridium catalysts have recently emerged as a good alternative to promote the isomerization of allylic alcohols in organic solvents [5c], their catalytic behavior in water has been scarcely evaluated. Only the dimer $[\{Ir(\mu\text{-}Cl)(cod)\}_2]$, combined with different water-soluble sulfonated or carboxylated phosphines, has been involved in such transformations and, unfortunately, proved to be poorly active, giving rise to low conversions (< 40%) [39f]. Palladium precursors $PdCl_2$ and $Pd(OAc)_2$ have also been associated with several hydrophilic mono- and di-phosphine ligands, affording carbonyl compounds in low to moderate yields [39b, f]. In addition, palladium-catalyzed isomerizations were observed as side-reactions during the hydrogenation of allylic alcohols promoted by $PdCl_2$ anchored on different polymers. Modulation of the catalytic system could favor the isomerization *vs.* hydrogenation, improving the selectivity up to 74% [41].

Poor to moderate selectivities, combined with low conversions, were also achieved in the nickel-catalyzed isomerization of geraniol (**16**) into citronellal (**17**) (Scheme 5) [42]. Under all the experimental conditions tested, variable amounts of linalool (**18**) (from 10% to 90%) were also generated through an undesired 1,3-rearrangement process. A similar observation was made using prenol as substrate. Note that the 1,3-rearrangement could be completely suppressed performing the catalytic reactions in an organic solvent, however, poor selectivities were still obtained due to the occurrence of competing cyclization, esterification and dehydration reactions.

2.3. Tandem processes

The development of one-pot processes involving multiple catalytic events has attracted a great deal of attention in recent years because of the practical and economic advantages of such reactions [43]. In this context, the ruthenium-catalyzed migration of the carbon-carbon double bond of allylic alcohols has been involved in a number of tandem processes in which the resulting carbonyl compound, or the corresponding enol intermediate, undergoes a subsequent transformation [5d]. In particular, reactions based on an isomerization/aldolization sequence have been extensively studied in organic solvents [8e, f, 10a, 44]. The *in-situ* generation of the enol or ketone reagent avoids the classical competing processes such as dimerization, polymerization and self-condensation. The first examples in aqueous media have been developed by Li and co-workers (Scheme 6) [45]. The use of $[RuCl_2(PPh_3)_3]$ afforded the cross-coupling between different allylic alcohols and aromatic aldehydes. Surprisingly, the formation of the aldol products

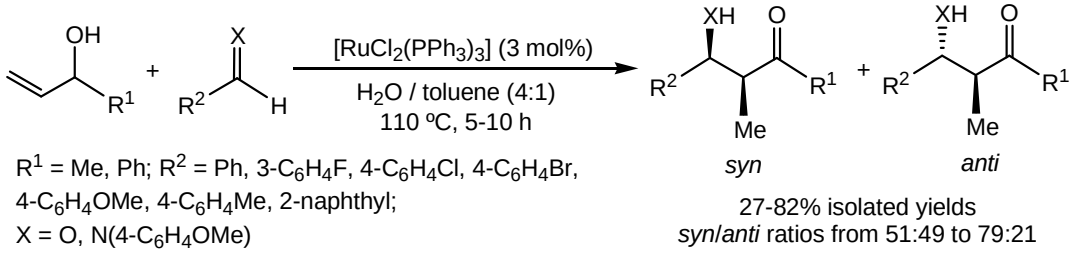


16 **17** **18**

yield up to 14%
17/**18** from 10/90 to 90/10

dppbts = tetrasulfonated 1,4-bis(diphenylphosphino)butane sodium salt

Scheme 5. Nickel-catalyzed isomerization of geraniol (**16**).



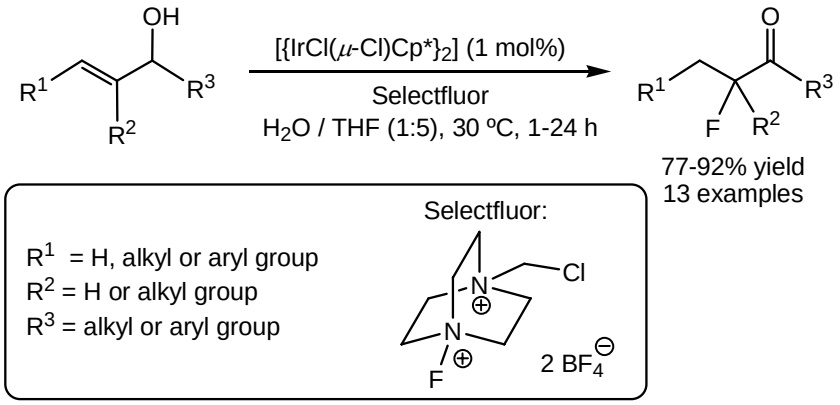
Scheme 6. Cross-couplings between allylic alcohols and aldehydes or imines.

only proceeded in biphasic H_2O/toluene mixtures and no reaction was observed in pure organic solvents or pure water. The first step of the catalytic reaction consists in the C=C bond migration of the alcohol, which is followed by the aldolization of the resulting enol. The participation of a ketone intermediate has been ruled out since no reaction takes place between propiophenone and benzaldehyde under the same conditions. Replacement of the aldehyde by an imine provided Mannich-type adducts, albeit only in moderate yields due to the partial hydrolysis of the imine [45b, c]. Note that the synthesis of β-aminoketones through the coupling of imines and allylic alcohols was then unprecedented. Although rather disappointing results were attained in aqueous media, a dramatic improvement was achieved performing the process in ionic liquids.

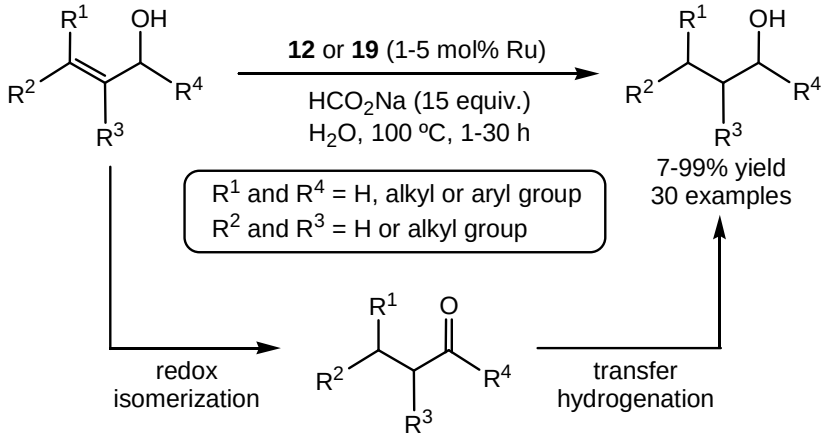
More recently, a highly efficient heterogeneous catalyst for these isomerization/adolization reactions has been reported by Uozumi and co-workers [46]. With this system, prepared by immobilization of the Ru(III) fragment [$RuCl_2$(η^5-C_5Me_5)] onto a phosphine-functionalized polystyrene-polyethyleneglycol resin, coupling between allylic alcohols and aldehydes readily took place in pure water. Even at low temperature (45ºC) and with a small metal loading (0.5 mol% Ru), good yields of the aldol products were obtained. Remarkably, *syn* isomers were predominant under neutral conditions (*syn*:*anti* ratio from 74:26 to 82:18), while formation of *anti* isomers prevailed upon addition of 20 mol% of K_2CO_3 (*syn*:*anti* ratio from 19:81 to 33:67). Finally, this heterogeneous catalyst could be recycled, at least in one further run, without loss of activity and diastereoselectivity.

In addition to aldehydes and imines, other electrophilic reagents could be involved in coupling processes. Thus, Martín-Matute and co-workers combined the isomerization of allylic alcohols with an electrophilic fluorination to synthesize α-fluoro ketones in good yields (Scheme 7) [47]. Best results were obtained in a biphasic THF/water mixture using [{IrCl(μ-Cl)Cp*}$_2$] (Cp* = η^5-C_5Me_5) as catalyst and Selectfluor® as the fluorine source. The reaction proceeded through an initial C=C bond migration, followed by fluorine addition to the corresponding metal-enolate intermediate. The C-F bond was formed exclusively at the alkenylic carbon of the starting allylic alcohol. This fact is really remarkable since usual synthetic methods, based on the fluorination of carbonyl compounds, rarely proceed with this high regiocontrol, addition taking place at both α-positions. However, we must note that variable amounts (5-30%) of the undesired non-fluorinated ketones were also generated as the result of the simple redox isomerization of the allylic alcohol.

On the other hand, Cadierno and co-workers recently developed a simple and highly efficient methodology for the selective reduction of the C=C bond in allylic alcohols, based on an unprecedented redox isomerization/transfer hydrogenation tandem process (Scheme 8) [48]. Thus, employing the mononuclear bis-allyl-ruthenium(IV) complex [$RuCl_2$(η^3:η^2:η^3-$C_{12}H_{18}$)] (**12** in Figure 5) or the hexamethylbenzene-ruthenium(II) dimer [{RuCl(μ-Cl)(η^6-C_6Me_6)}$_2$] (**19**) as catalyst, in the presence of an excess of sodium formate which acts both as a base and hydrogen source, a large variety of allylic alcohols were transformed into their corresponding saturated derivatives in moderate to excellent yields. Interestingly, substrates containing more than one C=C bond, such as the terpenoids nerol and



Scheme 7. Regioselective synthesis of α-fluoro ketones from allylic alcohols.



Scheme 8. Tandem process for the selective reduction of allylic alcohols in water.

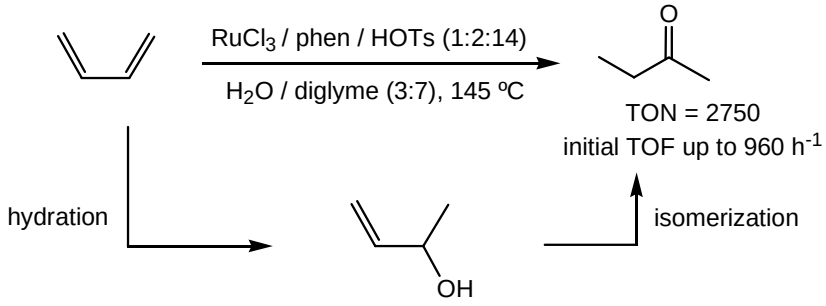
geraniol, could be regioselectively reduced in the α-position with respect to the alcohol group. Such selectivity is rarely observed in classical metal-catalyzed hydrogenations [49].

Although ruthenium(III)-based catalytic systems usually show low activities in the redox isomerization of allylic alcohols (see section 2.2.1.2), they represent the best alternative to promote the direct synthesis of methyl ethyl ketone (MEK) from butadiene [32, 33, 50]. This industrially relevant tandem process involves the initial hydration of butadiene, and a subsequent isomerization of the resulting allylic alcohol. In particular, the catalytic system $RuCl_3$/phen/HOTs allowed high rates (initial TOF up to 960 h^{-1}) and cumulative TON values up to 2750 after 10 h (Scheme 9).

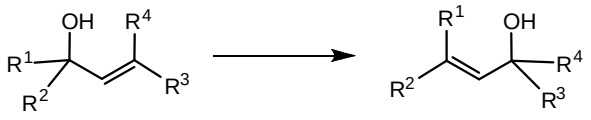
3. The 1,3-rearrangement of allylic alcohols

3.1. State of the art in organic media

In addition to the above-mentioned redox isomerizations allowing ketones or aldehydes formation, allylic alcohols can also undergo a 1,3-rearrangement in which both the hydroxyl group and the olefin are reshuffled (Scheme 10). This structural reorganization was traditionally promoted by superstoichiometric quantities of strong acids under harsh conditions [51]. Such experimental protocols usually result in poor yields and selectivities due to several competing reactions, especially in the case of substrates containing sensitive functional groups [52]. Dramatic improvements, both in terms of scope and selectivity, have been achieved recently with the use of transition metal catalysts [6, 53].



Scheme 9. Direct synthesis of MEK from butadiene.



Scheme 10. The 1,3-rearrangement of allylic alcohols.

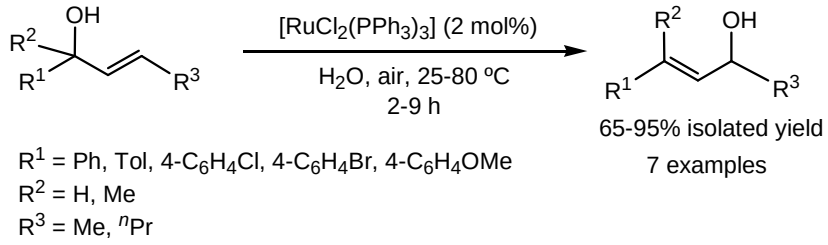
In particular, different oxo complexes of vanadium, tungsten, molybdenum, chromium and rhenium have been successfully employed [53]. Smoother conditions are then required, the transposition proceeding in some cases even at room temperature [54]. Moreover, metal-catalyzed 1,3-rearrangement of asymmetric allylic alcohols, with a stereogenic center at the initial C(OH) carbon atom, was found to occur with total enantioselectivity. Based on this property, selective formation of the alkaloid (-)-galanthamine has been achieved [55]. The 1,3-transposition has also found application in the flavors and fragrances industry enabling, for example, the direct synthesis of nerol and geraniol from linalool [56].

3.2. The 1,3-rearrangement of allylic alcohols in aqueous media

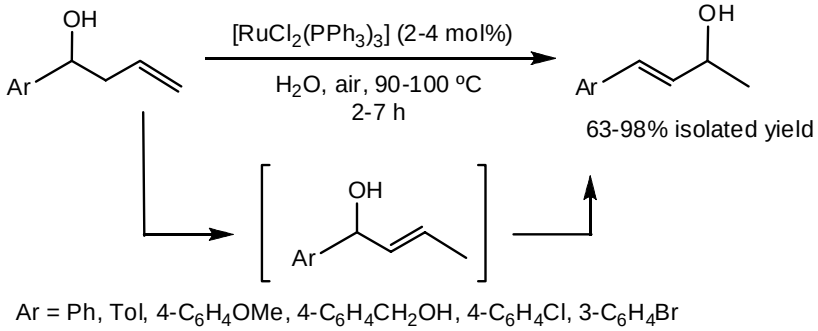
Reorganization of 1-phenylpropanol, an allylic alcohol with terminal C=C bond, into cinnamyl alcohol was observed in water at 80ºC in the presence of the rhodium complexes [{Rh(μ-Cl)(cod)}$_2$] or [Rh(NCMe)$_2$(cod)][BF$_4$] [38]. Under these conditions, small quantities (8-14%) of 1-phenylpropanone were also generated through a redox isomerization process. Remarkably, ketone turned out to be the predominant product when a hydrophilic phosphine was added to the reaction mixture. Selectivity towards the 1,3-rearrangement notably enhances starting from allylic alcohols with an internal C=C unit. Thus, Li and co-workers have described the selective 1,3-transposition of several α-arylallylic alcohols using the commercially available ruthenium(II) complex [RuCl$_2$(PPh$_3$)$_3$] (Scheme 11) [57].

Interestingly, the transformations of secondary allylic alcohols (R^2 = H, in Scheme 11) also turned out to be highly stereoselective as the corresponding *E*-isomers were exclusively formed. However, *E*/*Z* mixtures were obtained from tertiary alcohols. The 1,3-rearrangement is a reversible process and almost complete conversions are attained only with α-arylallylic alcohols. In this case, the final product, which features a C=C double bond conjugated with the aromatic ring, is clearly more stable than the starting material. In contrast, aliphatic substrates are only partially converted, leading to equilibrium mixtures of the non-conjugated initial and final compounds (*ca.* 1:1 ratio). Worthy of note, these ruthenium-promoted 1,3-transpositions are only operative in aqueous media, suggesting that water is directly involved in the catalytic cycle. The direct participation of the water was also proposed in similar palladium-catalyzed processes [58]. For this latter case, experiments performed with ^{18}O-labeled water and different allylic alcohols evidenced the oxygen isotope scrambling between the solvent and the substrates.

Isomerization of α-aryl homoallylic alcohols into the corresponding conjugated allylic alcohols were also performed in water using [RuCl$_2$(PPh$_3$)$_3$] as catalyst (Scheme 12) [57]. This transformation involves a tandem process based



Scheme 11. The 1,3-rearrangement of allylic alcohols promoted by $[RuCl_2(PPh_3)_3]$.



Scheme 12. Ru-catalyzed isomerization of homoallylic alcohols in water.

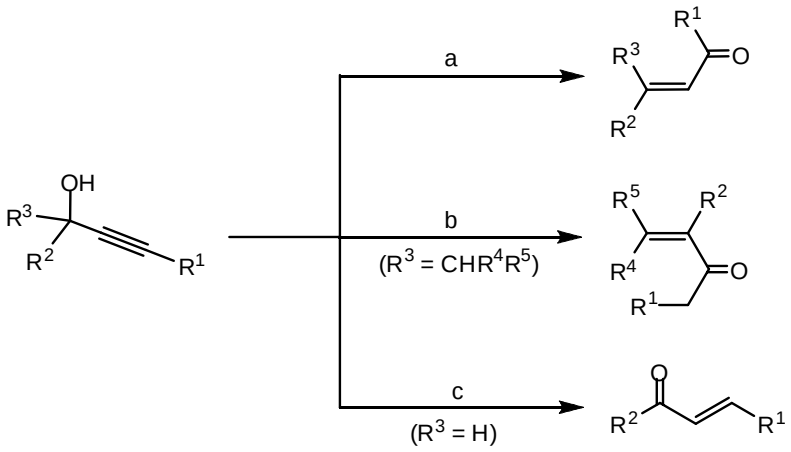
on an initial C=C bond migration and the subsequent 1,3-rearrangement. The reaction required more drastic conditions (higher metal loading and temperature) than those described for the 1,3-transposition alone (see Scheme 11). So, the initial olefin migration seems to be the rate limiting step. The harsher conditions used are probably responsible for the moderate selectivity. Indeed, in most of the cases, the desired conjugated allylic alcohol obtained was contaminated with the corresponding α-arylbutanone (alcohol/ketone ratio from 1.2:1 to >20:1). These byproducts result from the redox isomerization of the intermediates. On the other hand, in order to enable the recycling of the catalyst, complex $[RuCl_2(PPh_3)_3]$ was immobilized on various mesoporous structured materials [59]. These heterogeneous catalytic systems exhibited comparable activity and selectivity than their homogeneous counterpart and could be recycled up to seven times.

4. Isomerization of propargylic alcohols

4.1. State of the art in organic media

The isomerization reactions of propargylic alcohols provide straightforward synthetic routes to valuable and versatile α,β-unsaturated carbonyl compounds. The isomerization process can occur through three different reaction pathways (Scheme 13): the so-called Meyer-Schuster (path a) and Rupe (path b) rearrangements, in which a formal 1,3- or 1,2-shift of the hydroxyl group of the propargylic alcohol takes place, and the redox isomerization involving a simultaneous oxidation of the alcohol unit and reduction of the C≡C bond (path c). The Meyer-Schuster and Rupe reactions have been traditionally promoted by Brønsted acids under harsh conditions, leading usually to non-regioselective transformations [60]. In contrast, the redox isomerization is known to proceed smoothly under mild conditions in the presence of bases such as amines or phosphines [61]. However, the operability of this latter process is restricted to highly activated electron-deficient substrates (R^1 mainly an ester group).

As in the case of allylic alcohols, new synthetic approaches based on the use of metal catalysts, more selective and efficient under milder reaction conditions, have been developed further increasing the scope and synthetic value of these atom-economic transformations. Two review articles



Scheme 13. The three different reactions pathways for the isomerization of propargylic alcohols.

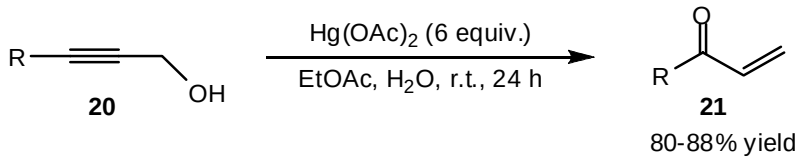
have appeared very recently giving complete overviews of the different catalysts presently available, their mechanisms of action, as well as relevant synthetic applications [7]. It is worthy of note that, with the gradual emergence of new catalysts, these isomerization processes have gained a prominent role within the toolbox of synthetic organic chemists, as clearly exemplified by their implication in the total synthesis of several natural products such as the arachidonic acid metabolite leukotriene B_4 [62], the antifungal agents sphingofungins E and F [63], the bioactive sesquiterpene lactone (+)-anthecotulide [64], or the carotenoids fucoxanthin and halocynthiaxanthin [65]. Remarkable results have also been recently obtained by several groups in tandem processes involving the combination of these isomerization processes with condensation [66], cyclocondensation [67], asymmetric hydrosilylation [68], Nazarov-type electrocyclization [69], Michael-type addition [70], oxirane ring-opening [71] and alkylation or arylation [72] reactions, all of them allowing the rapid access to elaborated structures from readily available propargylic alcohols.

Despite the growing interest in these metal-catalyzed isomerization reactions, efforts devoted to develop catalytic systems able to operate in aqueous environments have been scarce. In fact, only a very limited number of catalysts active in the Meyer-Schuster rearrangement of propargylic alcohols have been described up to now in the literature (some Rupe and Meyer-Schuster rearrangements have also been performed in water, under supercritical conditions, without the aid of metal complexes [73]).

4.2. Meyer-Schuster rearrangements in aqueous media

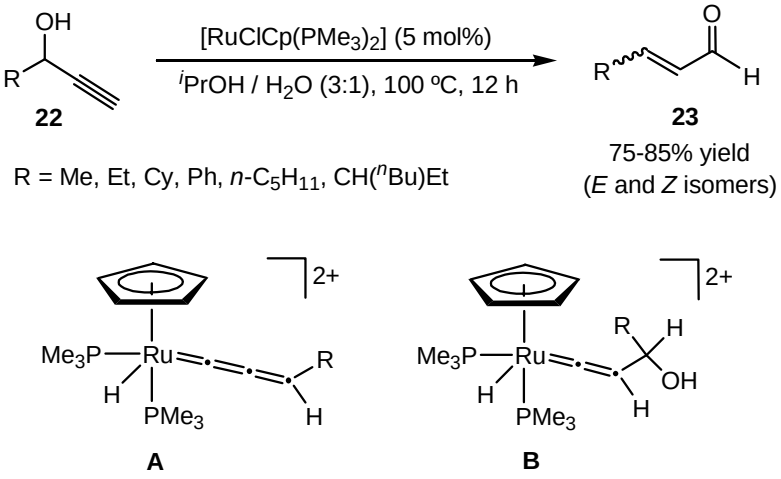
Toxic mercury(II) salts were employed in early reports [74]. However, the use of excess of the reagent was usually required as exemplified in the room-temperature Meyer-Schuster rearrangement of the primary propargylic alcohols **20** into the vinyl ketones **21**, which proceeded only in the presence of a six-fold excess of $Hg(OAc)_2$ (Scheme 14) [74e].

A more appealing approach was described by Wakatsuki and co-workers employing the cyclopentadienyl-ruthenium(II) derivative [RuClCp$(PMe_3)_2$] as catalyst [75]. Thus, as shown in Scheme 15, an array of enals **23** could be selectively obtained in high yields from the corresponding secondary propargylic alcohols **22** with 5 mol% of this ruthenium complex, in a 2-propanol/water (3:1) mixture at 100ºC. An anti-Markovnikov hydration of the alkyne moiety with concomitant dehydration of the original hydroxyl group was proposed by the authors as a possible reaction pathway. Moreover, they also suggested that nucleophilic addition of water to the electrophilic C_α atom of the hydride-ruthenium(IV) allenylidene **A** or hydroxy-vinylidene intermediate **B** could be involved in the hydration step [76]. Remarkably, although this aqueous transformation proceeded cleanly under neutral conditions, it presents an important



R = $(CH_2)_5Me$, $(CH_2)_2OBn$, CH_2OTHP, $(CH_2)_9OH$, $(CH_2)_9OMe$, $(CH_2)_9OTHP$

Scheme 14. $Hg(OAc)_2$-mediated isomerization of primary propargylic alcohols.



Scheme 15. Ru-catalyzed Meyer-Schuster rearrangement of secondary propargylic alcohols.

limitation concerning the nature of the alkynol since tertiary propargylic alcohols were completely unreactive under these conditions. In addition, it is also worth to note that, using this methodology, enals are in all cases generated as mixtures of the corresponding *E* and *Z* stereoisomers, with the former being predominant (*E*/*Z* ratios from 80:20 to 93:7).

Formation of variable amounts of *α,β*-unsaturated carbonyl compounds, *via* competitive Meyer-Schuster pathways, was also observed by Hintermann and Bressan during their studies on the catalytic hydration of the C≡C bond of propargylic alcohols by related cyclopentadienyl-ruthenium(II) complexes $[RuCp(NCMe)(PR_3)_2][PF_6]$ (PR_3 = functionalized pyridyl-phosphine) [77], as well as water-soluble ruthenium sulphophthalocyanines [78] and heterogeneous ruthenium hydroxyapatite species [78]. Unfortunately, no further studies were undertaken by the authors to obtain selective processes allowing the exclusive formation of the *α,β*-unsaturated carbonyl compounds.

Gold complexes have emerged in recent years as the most promising and effective catalysts for Meyer-Schuster rearrangements [7, 79]. In this context, the catalytic activity of a series of Au(I) complexes containing *N*-heterocyclic carbene (NHC) ligands **24a-c** (Figure 7) in aqueous environments has been described by Nolan and co-workers [80].

Best results were obtained with complex [AuCl(IPr)] (**24c**; IPr = *N,N'*-bis(2,6-diiso propylphenyl)imidazol-2-ylidene) which, associated with $AgSbF_6$ (2 mol% of each), was able to promote efficiently the isomerization of a broad range of secondary and tertiary propargylic alcohols in a 2:1 $MeOH/H_2O$ mixture at 60ºC, with a good to excellent *E*-stereoselectivity in the case of the secondary alkynols. However, while being able to accommodate sterically demanding and deactivating substituents, this catalytic system proved to be inappropriate for primary alcohols and substrates containing a terminal alkyne unit. From a mechanistic point of view, it was proposed

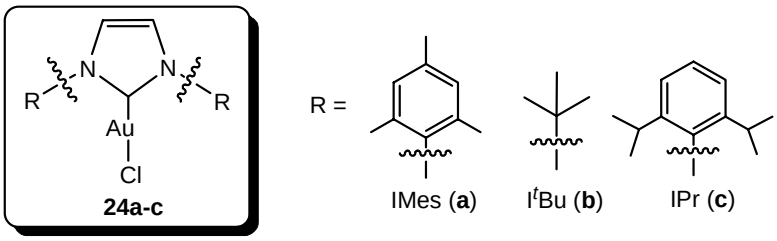
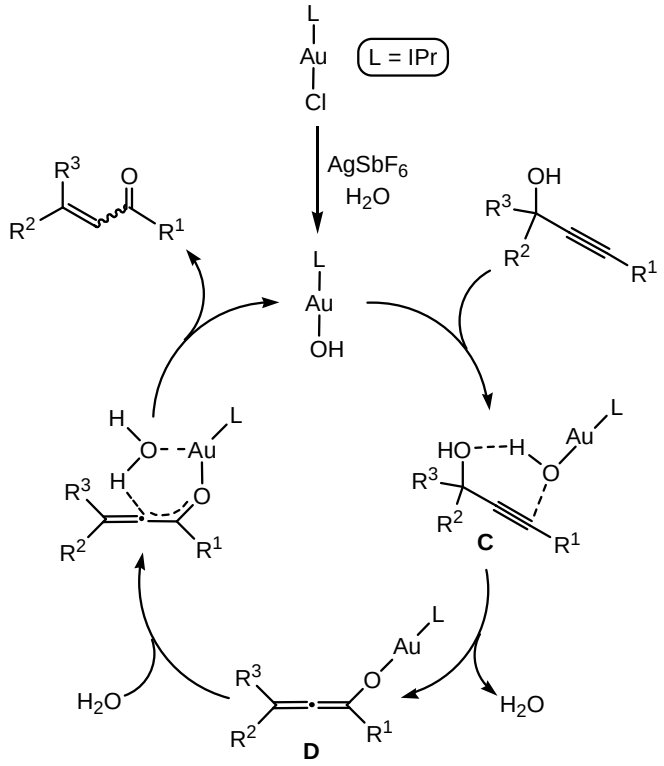
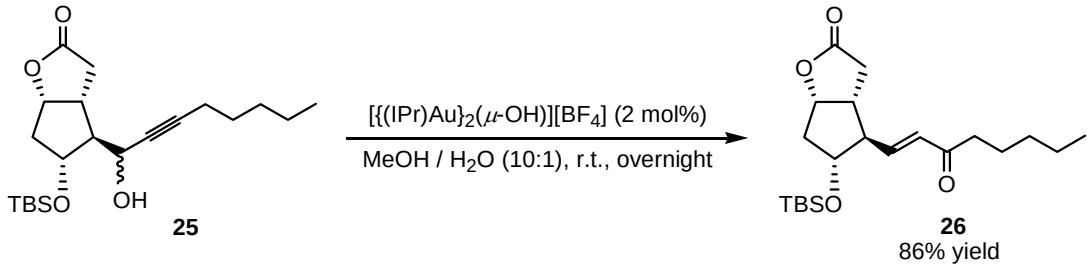


Figure 7. Structure of the NHC-Au(I) catalysts **24a-c**.

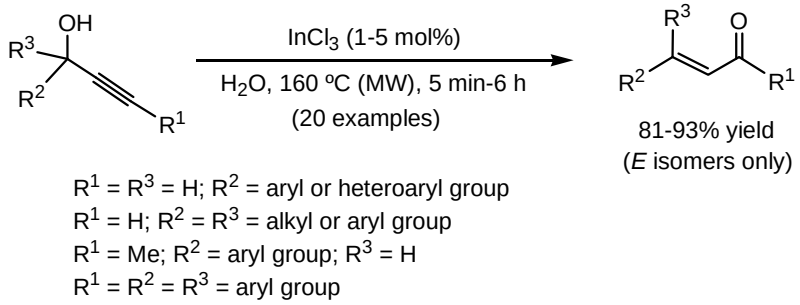


Scheme 16. Proposed mechanism of action of the NHC-Au(I) complex **24c**.

that **24c** activates a molecule of the water co-solvent to form a gold-hydroxo intermediate [Au(OH)(IPr)] (Scheme 16). This hydroxy species can then attack the triple bond of the alkynol to give **C**, which by elimination of water evolves into the allenolate **D**. Interaction of this last intermediate **D** with another water molecule regenerates the catalyst with release of the reaction product. To support this mechanistic hypothesis, [Au(OH)(IPr)] was targeted for synthesis and recently isolated and fully characterized [81]. However, the catalytic activity of [Au(OH)(IPr)] in the Meyer-Schuster rearrangement was found to be only modest [82]. Further studies by the same group permitted the isolation of the dinuclear hydroxo-complex [{(IPr)Au}$_2$(μ-OH)][BF_4] which conversely showed a remarkable activity in the isomerization process, thus suggesting its involvement as the real active species in aqueous media [82]. The synthetic utility of this dinuclear complex was fully evidenced by the successful isomerization of alkynol **25** into enone **26** as a key step in the synthesis of some prostaglandin derivatives (Scheme 17) [82a].



Scheme 17. Gold-catalyzed Meyer-Schuster rearrangement of the functionalized alkynol **25**.



Scheme 18. $InCl_3$-catalyzed Meyer-Schuster rearrangements in pure aqueous medium.

Besides the above-mentioned ruthenium- and gold-based catalysts, the inexpensive Lewis acid $InCl_3$ proved also useful for these isomerization processes. In particular, taking advantage of the solubility of $InCl_3$ in water, a simple, general, stereoselective (only *E*-isomers starting from secondary alcohols) and efficient protocol for the Meyer-Schuster rearrangement of propargylic alcohols into *α*,*β*-unsaturated carbonyl compounds in a pure aqueous medium could be developed (Scheme 18) [83]. Microwave irradiation was used as the heating source, and the catalyst could be recycled in three consecutive runs after selective extraction of the final enals or enones with diethyl ether. The only limitation of this method concerns the use of primary propargylic alcohols which led to polymeric materials formation. As in the case of gold complexes, the reaction was believed to proceed through an indium-hydroxo derivative which acts as the active species in the catalytic cycle.

5. SUMMARY AND FUTURE OUTLOOK

Atom-economical reactions are a prime focus of interest in modern chemical research. In this context, the availability of efficient methods for the conversion of allylic and propargylic alcohols into their isomeric carbonyl compounds is highly desirable, owing to the ease of preparation of the starting materials and the broad utility of the products in synthesis. In contrast to the limited practical utility of classical strategies, often requiring harsh conditions, strong acidic/basic media or multi-step sequences, metal-catalyzed isomerizations have emerged as more appealing and reliable alternatives since they usually operate under milder conditions and with higher levels of efficiency and selectivity.

On the other hand, the urgent demand for environmentally benign alternatives to volatile and toxic organic solvents has gained much attention in recent years in view of the increasing importance of Green Chemistry. In this mini-review article we have attempted to present the reader with an overview of the progress achieved on the catalytic isomerization of allylic and propargylic alcohols in environment-friendly aqueous media through an up-to-date discussion of the published literature. Thus, concerning the catalytic isomerization of allylic alcohols in water,

a number of efficient methodologies have already seen the light mainly by the aid of ruthenium and rhodium catalysts. However, it is apparent that a lot of progress remains to be made as practical applications of these methodologies for the synthesis of complex molecules, such as the total synthesis of natural products, have yet to be found. For their side, the transformations of propargylic alcohols in water have been comparatively much less developed, being presently limited to Meyer-Schuster processes. Obviously, the field remains open, and the discovery of catalytic systems allowing the development of Rupe and redox isomerization reactions in aqueous media is expected in the near future. We hope that this contribution serves to stimulate the research in these challenging directions.

6. ACKNOWLEDGEMENTS

Financial support from the Spanish MICINN (Projects CTQ2010-14796/BQU, CTQ2009-08746/BQU and CSD2007-00006) is acknowledged. S.E.G.-G. and J.G.-A. also thank MICINN and the European Social Fund for the award of "Ramón y Cajal" contracts.

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