Ruthenium-catalyzed reduction of allylic alcohols: An efficient isomerization/transfer hydrogenation tandem process

Victorio Cadierno,* Javier Francos, José Gimeno* and Noel Nebra

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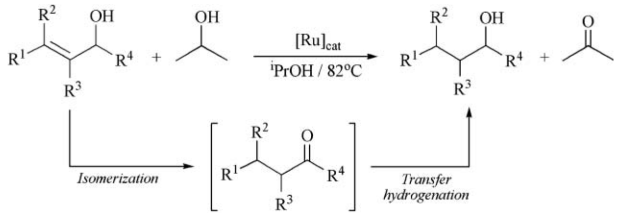
A simple and highly efficient method for the selective reduction of the C=C bond in allylic alcohols has been developed using the ruthenium(II) catalyst [{RuCl(μ-Cl)(η^6-C$_6$Me$_6$)}$_2$].

Ruthenium-catalyzed processes have become one of the most preferred methodologies in organic synthesis because of their highly efficient performance and versatile applications.[1] Among their most innovative synthetic approaches, a number of one-pot processes involving multiple chemical transformations (tandem catalysis) have recently appeared.[2,3]

Herein, we report a simple and highly efficient method for the selective reduction of the C=C bond in allylic alcohols, based on a novel ruthenium-catalyzed tandem process (Scheme 1). This one-pot transformation involves the initial isomerization of the allylic alcohol and subsequent transfer hydrogenation (TH) of the resulting carbonyl compound. A series of ruthenium complexes are well known catalysts for performing both individual steps with high efficiency.[4,5] The overall transformation, depicted in Scheme 1, represents an appealing alternative to classical transition metal-catalyzed C=C hydrogenations (Ru, Rh and Ir catalysts)[6] since (i) it takes place under relatively mild conditions and (ii) propan-2-ol is used as both the solvent and hydrogen source, avoiding the use of H_2 gas.

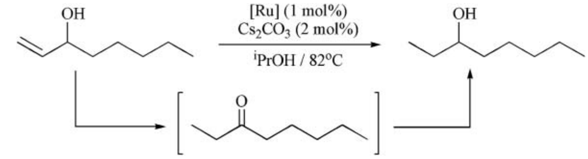
Firstly, as a model reaction, we checked the catalytic activity of several ruthenium complexes in the reduction of 1-octen-3-ol to octan-3-ol (Table 1). Ru(II) (Table 1, entries 1–10), Ru(III) (Table 1, entry 11) and Ru(IV) (Table 1, entries 12–13) derivatives were each tested as catalyst precursors. Thus, we have found that, under optimized conditions (1 mol% of Ru, 2 mol% of Cs_2CO_3,[7] 0.1 M solution of the substrate in propan-2-ol, 82 °C), total consumption of 1-octen-3-ol (>99% conversion, GC-determined) takes place within 9 h, independent of the ruthenium source employed. In particular, the best results were obtained using the hexamethylbenzene-Ru(II) dimer [{RuCl(μ-Cl)(η^6-C$_6$Me$_6$)}$_2$], which lead to the almost quantitative formation of the desired saturated alcohol after only 3.5 h (TOF = 28 h^{-1}; Table 1, entry 1). For the rest of the catalysts, variable amounts of the intermediate carbonyl compound, *i.e.* octan-3-one, were still detected in the reaction media after 9 h (Table 1, entries 2–13).



Scheme 1 Reduction of allylic alcohols through an isomerization/TH tandem process.

Remarkably, the efficiency shown by [{RuCl(μ-Cl)(η^6-C$_6$Me$_6$)}$_2$] in the reduction of 1-octen-3-ol is far higher than that of the bis(allyl)-ruthenium(IV) derivatives [RuCl$_2$(η^3:η^2:η^3-C$_{12}$H$_{18}$)] (C$_{12}$H$_{18}$ = dodeca-2,6,10-triene-1,12-diyl) 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), which, when associated with Cs_2CO_3, are among the most active ruthenium catalysts reported to date for allylic alcohol isomerization (Table 1: entry 1 *vs.* entries 12–13).[8] This fact clearly indicates that the transfer hydrogenation of the intermediate carbonyl compound is the rate limiting step of this tandem process. In accord with this, monitoring the catalytic reduction of 1-octen-3-ol to octan-3-ol, catalyzed by [{RuCl(μ-Cl)(η^6-C$_6$Me$_6$)}$_2$], by GC (Fig. 1) shows that the initial isomerization step takes place readily (*ca.* 15 min) to

Table 1 Reduction of 1-octen-3-ol catalyzed by Ru in the presence of Cs_2CO_3[a]



Entry	Catalyst	Time/h	Conversion (%)	Yield (%)[b]
1	[{RuCl(μ-Cl)(η^6-C$_6$Me$_6$)}$_2$]	3.5	>99	99
2	[{RuCl(μ-Cl)(η^6-1,3,5-C$_6$H$_3$Me$_3$)}$_2$]	6	>99	95
3	[{RuCl(μ-Cl)(η^6-*para*-cymene)}$_2$]	9	>99	91
4	[{RuCl(μ-Cl)(η^6-C$_6$H$_6$)}$_2$]	9	>99	75
5	[RuCl$_2$(PPh$_3$)$_3$]	9	>99	92
6	[Ru(η^3-2-C$_3$H$_4$Me)$_2$(COD)]	9	>99	35
7	[{RuCl$_2$(COD)}$_n$]	9	>99	26
8	[RuCl$_2$(DMSO)$_4$]	9	>99	16
9	[RuCl(η^5-C$_5$H$_5$)(PPh$_3$)$_2$]	9	>99	1
10	[RuCl(η^5-C$_9$H$_7$)(PPh$_3$)$_2$]	9	>99	4
11	RuCl$_3$·*n*H$_2$O	9	>99	3
12	[RuCl$_2$(η^3:η^2:η^3-C$_{12}$H$_{18}$)]	9	>99	94
13	[{RuCl(μ-Cl)(η^3:η^3-C$_{10}$H$_{16}$)}$_2$]	9	>99	86

[a] Reactions performed under a N_2 atmosphere at 82 °C using 2 mmol of 1-octen-3-ol (0.1 M in propan-2-ol). [Substrate] : [Ru] : [Cs_2CO_3] ratio = 100 : 1 : 2. [b] Yield of octan-3-ol determined by GC. The difference between conversion and octan-3-ol yield corresponds to the intermediate octan-3-one present in the reaction medium.

Departamento de Química Orgánica e Inorgánica, Instituto Universitario de Química Organometálica "Enrique Moles" (Unidad Asociada al C.S.I.C.), Universidad de Oviedo, 33071, Oviedo, Spain. E-mail: vcm@uniovi.es; jgh@uniovi.es; Fax: +34 985103446; Tel: +34 985103461

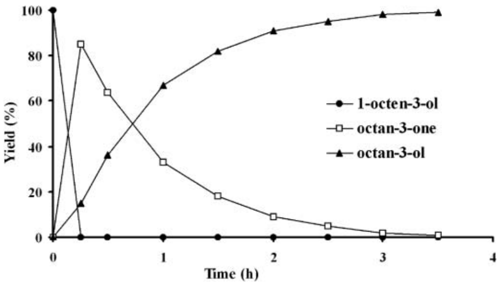


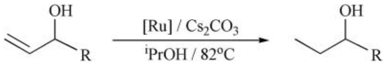
Fig. 1 Product distribution as a function of time for the reduction of 1-octen-3-ol catalyzed by [{RuCl(μ-Cl)(η^6-C_6Me_6)}$_2$].

afford octan-3-one, which slowly evolves into the final saturated alcohol (quantitative yield after 3.5 h).

The dimeric Ru(II) complex [{RuCl(μ-Cl)(η^6-C_6Me_6)}$_2$] is also very efficient in the reduction of a large number of allylic alcohols, proving the scope and synthetic utility of this catalytic transformation.† Nevertheless, its activity is strongly dependent on the substitution of the carbon–carbon double bond of the substrate employed.[9] Thus, as observed for 1-octen-3-ol, other monosubstituted allylic alcohols can be also reduced in almost quantitative yields using low ruthenium loadings (1–2 mol%, see entries 1–11 in Table 2).‡ Only when the coordinating furyl group was present in the molecule was a higher catalyst charge (5 mol% of Ru) required (Table 2, entry 12). Remarkably, the reduction of the two C=C bonds of the bis(allylic alcohol) **1** could be also completely achieved in 24 h, affording 1,3-bis(1-hydroxypropyl)benzene in 88% isolated yield (Scheme 2).

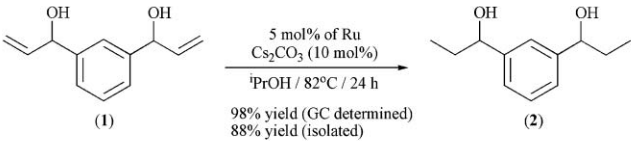
Di- and tri-substituted allylic alcohols are also reduced to the corresponding saturated alcohols in >90% yield using higher ruthenium loadings (3–5 mol%, see Table 3). Only the disubstituted species 3-penten-2-ol (Table 3, entry 1) and 2-methyl-2-propen-1-ol (Table 3, entry 7), both containing the less sterically demanding methyl group on the C=C bond, could be efficiently reduced using a ruthenium charge of 1 mol%. It is also interesting to note the chemoselectivity shown by complex [{RuCl(μ-Cl)(η^6-C_6Me_6)}$_2$] in the reduction of geraniol (Table 3, entry 13). Thus, although this

Table 2 Reduction of monosubstituted allylic alcohols catalyzed by Ru in the presence of Cs_2CO_3[a]



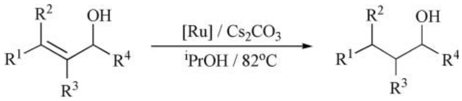
Entry	R	Ru (mol%)	Time/h	Conversion (%)	Yield (%)[b]
1	H	1	5.5	>99	99
2	Me	1	5.5	>99	98
3	Et	1	3	>99	97
4	^{n}Pr	1	3.5	>99	99
5	^{n}Bu	1	3	>99	97
6	Bn	1	22	>99	98
7	Ph	1	10	>99	97
8[c]	4-C_6H_4OMe	1	22	>99	90
9	3-C_6H_4OMe	2	15	>99	99
10	4-C_6H_4F	2	24	>99	99
11	4-C_6H_4Cl	2	24	>99	99
12	2-Furyl	5	5	>99	98

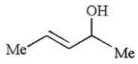
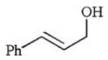
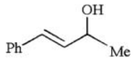
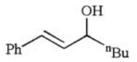
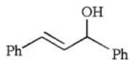
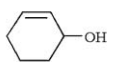
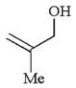
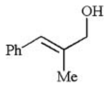
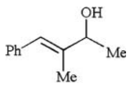
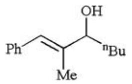
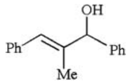
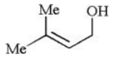
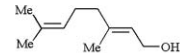
[a] Reactions performed under a N_2 atmosphere at 82 °C using 2 mmol of the corresponding allylic alcohol (0.1 M in propan-2-ol). [Ru] : [Cs_2CO_3] ratio = 1 : 2. [b] Yield of the saturated alcohol determined by GC. The difference between conversion and yield corresponds to the intermediate carbonyl compound present in the reaction medium. [c] *ca.* 8% of 1-methoxy-4-propylbenzene was also formed.



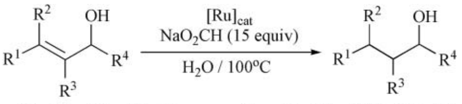
Scheme 2 Reduction of **1** catalyzed by [{RuCl(μ-Cl)(η^6-C_6Me_6)}$_2$].

Table 3 Reduction of allylic alcohols containing substituted C=C bonds catalyzed by Ru in the presence of Cs_2CO_3[a]



Entry	Substrate	Ru (mol%)	Time/h	Conversion (%)	Yield (%)[b]
1		1	9	>99	97
2		5	3	>99	99
3		3	7.5	>99	97
4		5	9	>99	90
5		5	22	>99	91
6		3	25	>99	99
7		1	9	>99	92
8		5	9	>99	98
9		5	6	>99	96
10		5	9.5	>99	93
11		5	9	>99	93
12		5	5	>99	90
13		5	24	>99	97

[a] Reactions performed under a N_2 atmosphere at 82 °C using 2 mmol of the corresponding allylic alcohol (0.1 M in propan-2-ol). [Ru] : [Cs_2CO_3] ratio = 1 : 2. [b] Yield of the saturated alcohol determined by GC. The difference between conversion and yield corresponds to the intermediate carbonyl compound present in the reaction medium.



$R^1 = R^2 = R^3 = R^4 = H$	(1 mol% of Ru, 99% yield, 6 h)
$R^1 = Me; R^2 = R^3 = R^4 = H$	(1 mol% of Ru, 96% yield, 9 h)
$R^1 = Ph; R^2 = R^3 = R^4 = H$	(1 mol% of Ru, 99% yield, 6 h)
$R^1 = R^2 = R^4 = H; R^3 = Me$	(5 mol% of Ru, 97% yield, 6 h)
$R^1 = Ph; R^2 = R^4 = H; R^3 = Me$	(5 mol% of Ru, 99% yield, 5 h)
$R^1 = R^2 = Me; R^3 = R^4 = H$	(5 mol% of Ru, 99% yield, 9 h)

Scheme 3 Reduction of allylic alcohols using water as the solvent.

compound presents two carbon–carbon double bonds, only isomerization of the C=C in α-position with respect to the alcohol group takes place, affording 3,7-dimethyl-6-octen-1-ol selectively.

Transition metal-catalyzed organic transformations in aqueous media have attracted much attention in recent years since, from an environmental perspective, water is the most benign and inexpensive solvent known.[10] This fact prompted us to explore the ability of complex $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}C_6Me_6)\}_2]$ to perform the reduction of allylic alcohols in water using sodium formate as the hydrogen source (Scheme 3).[11]§ The preliminary results seem to indicate that, in spite of the insolubility of the catalyst in water, the reduction of the substrates can also be efficiently performed in aqueous media.[12] Close examination of the reaction mixtures showed that they were emulsions rather than homogeneous solutions, the catalytic reaction probably taking place at the interface.

In summary, an operationally simple and highly efficient procedure for selective reduction of the C=C bond of allylic alcohols has been developed. This one-pot catalytic transformation, using the readily available ruthenium(II) dimer $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}C_6Me_6)\}_2]$, is based on an unprecedented tandem process involving the initial isomerization of the allylic alcohol into the corresponding carbonyl compound and subsequent transfer hydrogenation of the latter. We are confident that this simple methodology will be of interest to a wide range of synthetic organic chemists since: (i) it represents an appealing alternative to classical C=C hydrogenation using $H_{2(g)}$[6,12] and (ii) provides an efficient synthetic approach that allows the use of aqueous reaction media. Efforts to assess the scope, limitations and mechanism of this catalytic reaction are now in progress. The intriguing ability of the water-insoluble precatalyst $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}C_6Me_6)\}_2]$ to efficiently promote the tandem process in aqueous media deserves a more detailed study.

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Notes and references

† *General procedure for the catalytic reactions:* In a Schlenk flask fitted with a condenser, the corresponding allylic alcohol (2 mmol), the ruthenium catalyst precursor $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}C_6Me_6)\}_2]$ (0.01–0.05 mmol, 1–5 mol% of Ru) and Cs_2CO_3 (0.04–0.2 mmol, 2–10 mol%) were dissolved in propan-2-ol (20 mL) under an inert atmosphere. The reaction mixture was then stirred at 82 °C for the indicated time, the course of the reaction being monitored by regular sampling and analysis by GC. The identity of the resulting saturated alcohols, as well as the carbonyl intermediates, was assessed by comparison with commercially available, or independently synthesized (following reported procedures), pure samples and by their GC/MS fragmentation.

‡ We note that these reactions can be performed on a preparative scale. *Representative example:* Under a N_2 atmosphere, α-vinylbenzyl alcohol (2.68 g, 20 mmol), $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}C_6Me_6)\}_2]$ (0.067 g, 0.1 mmol), Cs_2CO_3 (0.132 g, 0.4 mmol) and propan-2-ol (200 mL) were introduced into a Schlenk flask and the reaction mixture stirred at 82 °C for 15 h (almost quantitative yield by GC). After removal of the solvent under vacuum, flash chromatography (silica gel) of the residue using a mixture of EtOAc/hexane (1 : 10) as eluent afforded 2.45 g (17.99 mmol) of analytically pure 1-phenyl-1-propanol (90% yield).

§ *General procedure for the catalytic reactions in water:* In a sealed tube, the corresponding allylic alcohol (5 mmol), $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}C_6Me_6)\}_2]$ (0.025–0.125 mmol, 1–5 mol% of Ru) and NaO_2CH (5.15 g, 75 mmol) were mixed in water (10 mL) under an inert atmosphere. The reaction mixture was then stirred at 100 °C for the indicated time.

1 (*a*) *Ruthenium Catalysts and Fine Chemistry*, ed. C. Bruneau and P. H. Dixneuf, Springer-Verlag, Berlin, 2004; (*b*) *Ruthenium in Organic Synthesis*, ed. S.-I. Murahashi, Wiley-VCH, Weinheim, 2004.

2 For a review on Ru-catalyzed tandem processes, see: C. Bruneau, S. Dérien and P. H. Dixneuf, *Top. Organomet. Chem.*, 2006, **19**, 295.

3 For a highly formative review on tandem catalysis, see: D. E. Fogg and E. N. dos Santos, *Coord. Chem. Rev.*, 2004, **248**, 2365.

4 For general reviews on the catalytic isomerization of allylic alcohols, see: (*a*) R. Uma, C. Crévisy and R. Grée, *Chem. Rev.*, 2003, **103**, 27; (*b*) R. C. van der Drift, E. Bouwman and E. Drent, *J. Organomet. Chem.*, 2002, **650**, 1. A number of highly efficient Ru catalysts have recently been described: (*c*) V. Cadierno, S. E. García-Garrido and J. Gimeno, *Chem. Commun.*, 2004, 232; (*d*) M. Ito, S. Kitahara and T. Ikariya, *J. Am. Chem. Soc.*, 2005, **127**, 6172; (*e*) B. Martín-Matute, K. Bogár, M. Edin, F. B. Kaynak and J.-E. Bäckvall, *Chem.–Eur. J.*, 2005, **11**, 5832; (*f*) V. Cadierno, S. E. García-Garrido, J. Gimeno, A. Varela-Álvarez and J. A. Sordo, *J. Am. Chem. Soc.*, 2006, **128**, 1360; (*g*) P. Crochet, M. A. Fernández-Zúmel, J. Gimeno and M. Scheele, *Organometallics*, 2006, **25**, 4846.

5 TH of carbonyl compounds is one of the most studied Ru-catalyzed transformations: (*a*) S. E. Clapman, A. Hadzovic and R. H. Morris, *Coord. Chem. Rev.*, 2004, **248**, 2201; (*b*) S. Gladiali and A. Alberico, *Chem. Soc. Rev.*, 2006, **35**, 226.

6 Examples of the metal-catalyzed hydrogenation of allylic alcohols can be found in: (*a*) H. Takaya, T. Ohta, S. Inoue, M. Katimura and R. Noyori, *Org. Synth.*, 1995, **72**, 74; (*b*) Y. Sun, C. Le Blond, J. Wang, D. G. Blackmond, J. Laquidara and J. R. Sowa, Jr., *J. Am. Chem. Soc.*, 1995, **117**, 12647; (*c*) D. G. Blackmond, A. Lightfoot, A. Pfaltz, T. Rosner, P. Schnider and N. Zimmermann, *Chirality*, 2000, **12**, 442.

7 Both individual steps, *i.e.* allylic alcohol isomerization and TH of the carbonyl intermediate, require the use of a base as a co-catalyst to promote the formation of the corresponding hydride–ruthenium complexes, which are the real catalytically active species in both transformations (see ref. 4 and ref. 5). Several bases (Li_2CO_3, Na_2CO_3, K_2CO_3, Cs_2CO_3, $LiOH{\cdot}H_2O$, NaOH, KOH, $CsOH{\cdot}H_2O$, NaO^tBu and KO^tBu) and [Ru] : [base] ratios (from 1 : 1 to 1 : 24) have been checked; the best results being obtained when Cs_2CO_3 was used as a co-catalyst (optimal [Ru] : $[Cs_2CO_3]$ ratios = 1 : 2, 1 : 3 and 1 : 4). As expected, low conversions (<15%) were observed in all cases in the absence of base.

8 Using $[RuCl_2(\eta^3{:}\eta^2{:}\eta^3\text{-}C_{12}H_{18})]$ and $[\{RuCl(\mu\text{-}Cl)(\eta^3{:}\eta^3\text{-}C_{10}H_{16})\}_2]$ as catalysts, TOF values of 429 h^{-1} and 3000 h^{-1}, respectively, were attained in the isomerization of 1-octen-3-ol into octan-3-one in refluxing THF (0.2 mol% Ru, 0.4 mol% of Cs_2CO_3). Under the same reaction conditions, $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}C_6Me_6)\}_2]$ lead to a TOF value of only 125 h^{-1}. See ref. 4f.

9 It is well known that the isomerization of allylic alcohols becomes more difficult as the number of substituents increases on the C=C double bond, requiring longer reaction times and/or higher catalyst loadings. See ref. 4.

10 For recent reviews, see: (*a*) C.-J. Li, *Chem. Rev.*, 2005, **105**, 3095; (*b*) C.-J. Li and L. Chen, *Chem. Soc. Rev.*, 2006, **35**, 68.

11 NaO_2CH is the most popular hydrogen source (it also acts as base) used in the aqueous TH of carbonyl compounds. See ref. 5.

12 (*a*) A related Ru-catalyzed isomerization/hydrogenation tandem process in an aqueous medium has been reported: P. Csabai and F. Joó, *Organometallics*, 2004, **23**, 5640; (*b*) The Ru-catalyzed reduction of alkenes using $NaBH_4$ has been recently described: G. R. A. Adair, K. K. Kapoor, A. L. B. Scolan and J. M. J. Williams, *Tetrahedron Lett.*, 2006, **47**, 8943.