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Efficient Redox Isomerization of Allylic Alcohols under Mild Conditions Catalyzed by Arene−Ruthenium(II) Complexes

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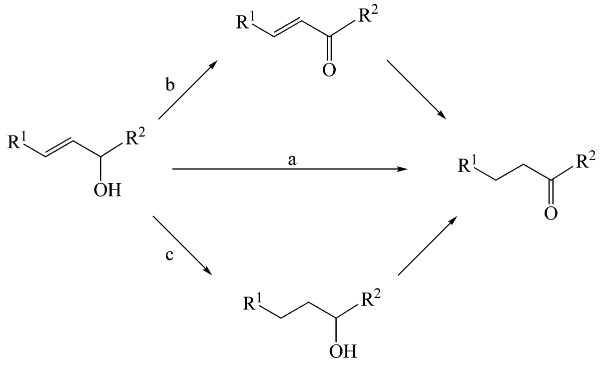
The catalytic activity of the arene−ruthenium(II) complexes $[RuCl_2(\eta^6\text{-}p\text{-cymene})(L)]$ (L = $P(OPh)_3$, $P(OMe)_3$, $P(OEt)_3$, PPh_3, $P(p\text{-}C_6H_4OMe)_3$, PMe_2Ph, PMe_3, PEt_3, PCy_3) in the isomerization of allylic alcohols into the corresponding saturated ketones has been investigated, the best performances being obtained using $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(OEt)_3\}]$. This compound has proven to be able to catalyze the transformation of poorly reactive substrates of the type $R^1CH{=}CHCH(OH)R^2$ and $R^1CH{=}C(R^2)CH(OH)R^3$ (R^1, R^2, $R^3 \neq H$) under very smooth conditions.

Introduction

Isomerization of allylic alcohols catalyzed by transition metal complexes represents a straightforward access to the corresponding carbonyl compounds (pathway a in Scheme 1), which conveniently replaces the conventional two-step organic procedures (pathway b or c).[1]

Scheme 1. Transformation of Allylic Alcohols into Saturated Carbonyl Compounds



Hence, during the last two decades considerable efforts have been devoted to develop efficient catalytic systems for this process. In this context, a great variety of group 6, 8, 9, and 10 metal complexes were found to be active, the best performances being obtained using iron, ruthenium, and rhodium compounds.[1,2] Nevertheless, only a few catalysts have proven to be efficient under mild conditions, and then, in most of the cases, temperatures ranging from 60 to 180 °C are required to reach reasonable conversions.[1] In particular, allylic alcohols bearing substituents on the carbon−carbon double bond, i.e., substrates of the type $R^1CH{=}CHCH(OH)R^2$, $CH_2{=}C(R^1)CH(OH)R^2$, $R^1CH{=}C(R^2)CH(OH)R^3$, or $(R^1)(R^2)C{=}CHCH(OH)R^3$ (R^1, R^2, $R^3 \neq H$),[3] are rarely isomerized under smooth temperature conditions and usually required high catalyst loadings and long reaction times. Among the most active catalysts for the isomerization of highly substituted allylic alcohols are those described by Ikariya and Bäckvall ($[RuCl(\eta^5\text{-}Cp^*)\{\kappa^2(P,N)\text{-}Ph_2PCH_2CH_2NH_2\}]$[2b] and $[RuCl(\eta^5\text{-}C_5Ph_4Me)(CO)_2]$,[2c] respectively), which, in the presence of KO^tBu, are able to transform a variety of functionalized allylic alcohols at ≤30 °C within a few hours. Recently, we have demonstrated that (η^6-arene)−ruthenium(II) complexes containing phosphinite, phosphonite, or phosphite ligands are also competitive catalysts.[2d] Indeed, the derivatives $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{\kappa^1(P)\text{-}Ph_2POCH_2CH_2NMe_2\}]$, $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{\kappa^1(P)\text{-}PhP(OCH_2CH_2NMe_2)_2\}]$, and $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{\kappa^1(P)\text{-}P(OCH_2CH_2NMe_2)_3\}]$ are able to promote the isomerization of unsubstituted allylic alcohols at 35 °C in only 5−30 min,[2d] although a higher temperature is required for the substituted ones. The electronic properties of the phosphorus ligands seem to have a great influence on the efficiency since only moderate activity was usually reported for other arene−ruthenium(II) derivatives.[4] Therefore, with the aim of designing new efficient catalytic systems for substituted allylic alcohols we decided to study the activity of a wide range of (η^6-arene)ruthenium(II) complexes of the type $[RuCl_2(\eta^6\text{-}p\text{-cymene})(L)]$. Their steric and electronic properties are easily tunable by changing the nature of the L ligand. Furthermore, they are readily accessible in gram-scale from the commercially available dimeric precursor $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})\}_2]$ and the corresponding P-donor ligand.[5]

We report here the excellent catalytic activity of $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(OEt)_3\}]$ (either isolated or prepared in situ) in the

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(1) For reviews on catalytic isomerization of allylic alcohols see: (a) van der Drift, R. C.; Bouwman, E.; Drent, E. *J. Organomet. Chem.* **2002**, *650*, 1. (b) Uma, R.; Crévisy, C.; Grée, R. *Chem. Rev.* **2003**, *103*, 27.

(2) For recent examples of efficient catalytic systems see: (a) Cadierno, V.; García-Garrido, S. E.; Gimeno, J. *Chem. Commun.* **2004**, 232. (b) Ito, M.; Kitahara, S.; Ikariya, T. *J. Am. Chem. Soc.* **2005**, *127*, 6172. (c) Martín-Matute, B.; Bogár, K.; Edin, M.; Kaynak, F. B.; Bäckvall, J.-E. *Chem. Eur. J.* **2005**, *11*, 5832. (d) Crochet, P.; Díez, J.; Fernández-Zúmel, M. A.; Gimeno, J. *Adv. Synth. Catal.* **2006**, *348*, 93. (e) Cadierno, V.; García-Garrido, S. E.; Gimeno, J.; Varela-Álvarez, A.; Sordo, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 1360.

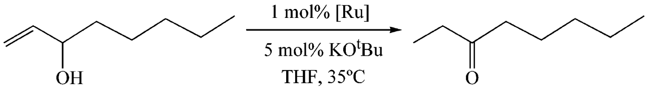
(3) No example has been described yet for the isomerization of allylic alcohols of the type $(R^1)(R^2)C{=}C(R^3)CH(OH)R$.[4]

(4) (a) Bäckvall, J.-E.; Andreasson, U. *Tetrahedron Lett.* **1993**, *34*, 5459. (b) Cadierno, V.; Crochet, P.; García-Garrido, S. E.; Gimeno, J. *Dalton Trans.* **2004**, 3635. (c) Takai, Y.; Kitaura, R.; Nakatani, E.; Onishi, T.; Kurosawa, H. *Organometallics* **2005**, *24*, 4729. (d) Fekete, M.; Joó, F. *Catal. Commun.* **2006**, *7*, 783. (e) Díaz-Álvarez, A. E.; Crochet, P.; Zablocka, M.; Duhayon, C.; Cadierno, V.; Gimeno, J.; Majoral, J. P. *Adv. Synth. Catal.* **2006**, *348*, 1671.

(5) Le Bozec, H.; Touchard, D.; Dixneuf, P. H. *Adv. Organomet. Chem.* **1989**, *29*, 163.

10.1021/om060582e CCC: $33.50

Table 1. Isomerization of 1-Octen-3-ol into 3-Octanone Catalyzed by Complexes $[RuCl_2(L)(\eta^6$-*p*-cymene)][a]



entry	catalyst [L]	time (min)	yield (%)	TOF (h^{-1})[b]
1	**1a** $[P(OPh)_3]$	265	80	18
2	**1b** $[P(OMe)_3]$	35	99	170
3	**1c** $[P(OEt)_3]$	10	98	588
4	**1d** $[PPh_3]$	30	99	198
5	**1e** $[P(p\text{-}C_6H_4OMe)_3]$	65	99	91
6	**1f** $[PMe_2Ph]$	175	99	34
7	**1g** $[PMe_3]$	195	99	30
8	**1h** $[PEt_3]$	85	99	70
10	**1i** $[PCy_3]$	270	33	7

[a] Reactions carried out at 35 °C using 4 mmol of 1-octen-3-ol, 1 mol % of **1a**−**1i**, 5 mol % of KO^tBu, and 20 mL of THF. [b] Turnover frequency ((mol product/mol Ru)/time), calculated at the time indicated in each case.

isomerization of highly substituted allylic alcohols under smooth conditions. This catalyst is certainly the easiest to prepare and handle described to date.

Results and Discussion

To select the most efficient catalytic system, we have first evaluated the activity of the arene−ruthenium(II) complexes $[RuCl_2(\eta^6$-*p*-cymene)(L)] (L = $P(OPh)_3$ (**1a**), $P(OMe)_3$ (**1b**), $P(OEt)_3$ (**1c**), PPh_3 (**1d**), $P(p\text{-}C_6H_4OMe)_3$ (**1e**), PMe_2Ph (**1f**), PMe_3 (**1g**), PEt_3 (**1h**), PCy_3 (**1i**)) in the isomerization of a simple model, the 1-octen-3-ol (see Table 1). The reactions were performed at 35 °C using 4 mmol of substrate, 1 mol % of derivatives **1a**−**1i**, 5 mol % of KO^tBu, and 20 mL of THF.[6] The results obtained under these conditions are summarized in Table 1. In all cases, 1-octen-3-ol is selectively transformed into 3-octanone, the rate of the reaction strongly depending on the nature of the phosphorus-donor ligand (TOF from 7 to 588 h^{-1}). The highest efficiency is observed for complex **1c**, bearing a triethyl phosphite ligand (entry 3). As a general trend, the derivatives containing the most electron-withdrawing ligands (i.e., **1b**−**1d**; entries 2−4; TOF from 170 to 588 h^{-1}) present a higher activity than those with electron-rich ones (i.e., **1e**−**1i**; entries 5−9; TOF from 7 to 91 h^{-1}), with the exception being $[RuCl_2(\eta^6$-*p*-cymene)$\{P(OPh)_3\}]$ (**1a**), which displays only a limited efficiency (entry 1; TOF = 18 h^{-1}).

The isomerization of 1-octen-3-ol catalyzed by **1c** can also be successfully performed in acetonitrile, 1,4-dioxane, toluene, or water (Table 2; entries 2−6), quantitative conversions into 3-octanone being reached in 15−130 min. Nevertheless, no rate improvement is observed with respect to the reaction carried out in THF. The increase of the concentration also results in a slight drop in activity (Table 2; entries 6 and 7).

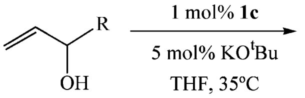
Remarkably, the in-situ-generated catalyst, obtained from the dimeric precursor $[\{RuCl(\mu\text{-}Cl)(\eta^6$-cymene)$\}_2]$ and a slight excess of triethyl phosphite (see details in the Experimental Section), presents catalytic performances similar to the isolated complex **1c** (Table 2, entry 8). This convenient one-pot procedure, based on the use of two commercial air- and moisture-stable reagents, without the need of any purification, may be particularly attractive for further application of this catalytic process in organic synthesis by nonexpert organometallic chemists.

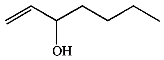
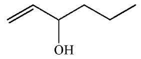
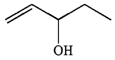
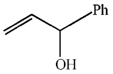
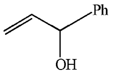
Table 2. Optimization of the Reaction Conditions[a]

entry	solvent	time (min)	yield (%)	TOF (h^{-1})[b]
1	THF	10	98	588
2	NCMe	15	98	392
3	1,4-dioxane	15	99	396
4	toluene	75	99	79
5	water	130	99	46
6[c]	THF	20	99	297
7[d]	THF	35	99	170
8[e]	THF	15	99	396

[a] Reactions carried out at 35 °C using 4 mmol of 1-octen-3-ol, 20 mL of solvent, 1 mol % of **1c**, and 5 mol % of KO^tBu. [b] Turnover frequency ((mol product/mol Ru)/time), calculated at the time indicated in each case. [c] Using 10 mL of THF. [d] Using 5 mL of THF. [e] Using the catalyst **1c** generated in situ.

Table 3. Isomerization of Different Monosubstituted Allylic Alcohols Catalyzed by Complex 1c[a]



Entry	Substrate	T (ºC)	Time (min)	Yield (%)	TOF (h^{-1})[b]
1		35	55	99	108
2		35	20	99	297
3		35	20	99	297
4		35	230	95	25
5		75	5	98	1176

[a] Reactions were carried out using 4 mmol of substrate, 20 mL of THF, 1 mol % of **1c**, and 5 mol % of KO^tBu. [b] Turnover frequency ((mol product/mol Ru)/time), calculated at the time indicated in each case.

To evaluate the scope and limitation of catalyst **1c**, the study has been extended to other substrates. As shown in Table 3, compound **1c** is also able to catalyze the isomerization of other allylic alcohols with a monosubstituted C=C bond, such as 1-hepten-3-ol, 1-hexen-3-ol, 1-penten-3-ol, and α-vinylbenzyl alcohol, under smooth conditions (1 mol % Ru, 35 °C, entries 1−4). In all cases, almost quantitative conversion was reached in 20−230 min. Noteworthy, the α-vinylbenzyl alcohol, known to be less reactive,[2a,e] is transformed into propiophenone after 230 min at 35 °C or in only 5 min at reflux temperature (entry 5 in Table 3).

More interestingly, the transformation of highly substituted allylic alcohols can also be catalyzed using complex **1c** (Table 4). In this case, the ruthenium loading needs to be increased from 1 to 5 mol % in order to overcome the lower reactivity of these substrates. Under these conditions, disubstituted allylic alcohols, namely, 4-phenylbut-3-en-2-ol, 1-phenylhept-1-en-3-ol, and 1,3-diphenylprop-2-en-1-ol, are quantitatively isomerized into the corresponding saturated ketones in 5−10 min (entries 1, 3, and 4). When the reaction is performed at higher temperature (75 °C), similar conversion was obtained with only 1 mol % of catalyst (entry 2, Table 4). The isomerization reaction can be scaled-up, affording multigrams of the corre-

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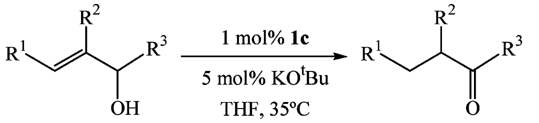
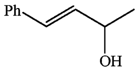
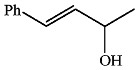
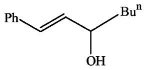
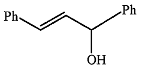
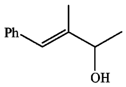
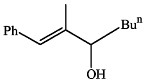
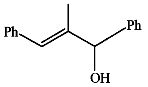
(6) In the absence of base no conversion is observed. The choice of KO^tBu is based on previous results obtained with arene−ruthenium(II) complexes (see ref 2d).

Table 4. Isomerization of Different Substituted Allylic Alcohols Catalyzed by Complex 1c[a]



Entry	Substrate	T (ºC)	Time (min)	Yield (%)	TOF (h^{-1})[b]
1		35	5	99	238
2[c]		75	10	99	494
3		35	10	99	119
4		35	5	97	233
5		35	35	99	34
6		35	50	99	24
7		35	25	99	48

[a] Unless otherwise noted, reactions were carried out using 4 mmol of substrate, 20 mL of THF, 5 mol % of **1c**, and 25 mol % of KO^{t}Bu. [b] Turnover frequency ((mol product/mol Ru)/time), calculated at the time indicated in each case. [c] Using 1 mol % of **1c** and 5 mol % of KO^{t}Bu.

sponding ketone (a representative example is shown in the Experimental Section).

Noteworthy, the trisubstituted substrates 3-methyl-4-phenylbut-3-en-2-ol, 2-methyl-1-phenylhept-1-en-3-ol, and 2-methyl-1,3-diphenylprop-2-en-1-ol are also readily converted at 35 °C in 25−50 min (entries 5−7). As far as we are aware, only two other catalytic systems, namely, [$Fe(CO)_5$][7] and RuCl(η^5-Cp*)-{κ^2(*P*,*N*)-$Ph_2PCH_2CH_2NH_2$}],[2b] are able to isomerize efficiently allylic alcohols with a trisubstituted C=C bond under smooth conditions.[8] However, the iron catalyst is of reduced practical application since besides its toxicity it is only active under irradiation conditions.[7] On the other hand, the ruthenium precursor also shows excellent efficiency,[2b] but the synthesis of the catalyst requires a multistep approach,[9] limiting its application as well.

Conclusions

It has been shown that the readily available half-sandwich ruthenium(II) complexes [$RuCl_2$(η^6-*p*-cymene)(L)] (L = $P(OPh)_3$, $P(OMe)_3$, $P(OEt)_3$, PPh_3, P(*p*-$C_6H_4OMe)_3$, PMe_2Ph, PMe_3, PEt_3, PCy_3) are good catalysts in the isomerization of allylic alcohols into the corresponding saturated ketones. In particular, the triethyl phosphite derivative [$RuCl_2$(η^6-*p*-cymene){$P(OEt)_3$}] presents an extremely high catalytic activity under smooth reaction conditions even in the transformation of allylic alcohols with a trisubstituted C=C bond, i.e., $R^1CH{=}C(R^2)CH(OH)R^3$ (R^1, R^2, $R^3 \neq$ H). It is noteworthy that only very few transition metal complexes are able to isomerize efficiently this type of substrate. The easy access to catalyst **1c** in gram-scale and its air- and moisture-stability provide a valuable tool to use in further organic transformations.

Experimental Section

The manipulations were performed under an atmosphere of dry nitrogen using vacuum-line and standard Schlenk techniques. Solvents were dried by standard methods and distilled under nitrogen before use. All reagents were obtained from commercial suppliers with the exception of compounds [{$RuCl_2$(η^6-arene)(L)] (L = $P(OPh)_3$, $P(OMe)_3$, $P(OEt)_3$, PPh_3, P(*p*-$C_6H_4OMe)_3$, PMe_2-Ph, PMe_3, PEt_3, PCy_3),[2d,10−13] *trans*-4-phenylbut-3-en-2-ol,[14] *trans*-1-phenylhept-1-en-3-ol,[15] and *trans*-2-methyl-1,3-diphenylprop-2-en-1-ol,[16] which were prepared by following the methods reported in the literature. GC and GC/MSD measurements were made on a Hewlett-Packard HP6890 apparatus (Supelco Beta-Dex 120 column; 30 m; 250 μm) and an Agilent 6890N apparatus coupled to a 5973 mass detector (HP-1MS column; 30 m; 250 μm), respectively.

Preparation of *trans*-2-Methyl-1-phenylhept-1-en-3-ol. To a solution of *trans*-α-methylcinnamaldehyde (2.8 mL, 20 mmol) in 60 mL of THF was added dropwise BuLi (1.6 M in hexane, 16 mL, 25.6 mmol) at −100 °C. After stirring for 30 min, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (50 mL), and the product was extracted three times with 50 mL of diethyl ether. Then, the organic phases were washed with 50 mL of water, dried over $MgSO_4$, filtered, and evaporated under vacuum, affording a yellowish oil. Yield: 3.455 g (84%). ^{1}H NMR, $CDCl_3$, δ: 7.39−7.23 (m, 5 H, ArH), 6.52 (s, 1 H, PhC*H*=), 4.19 (t, 1 H, $^3J_{HH}$ = 6.7, C*H*OH), 2.58 (s, 1 H, OH), 1.91 (s, 3 H, =CMe), 1.69 (m, 2 H, CH_2), 1.47−1.32 (m, 4 H, CH_2), 0.98 (t, 3 H, $^3J_{HH}$ = 7.0, CH_2Me). $^{13}C\{^1H\}$ NMR, $CDCl_3$, δ: 140.6 (s, C_{ipso}), 137.8 (s, =*C*Me), 129.0 and 128.1 (both s, C_{meta} and C_{ortho}), 126.4 and 125.7 (both s, Cp and =CH), 78.1 (s, CHOH), 34.8, 28.1 and 22.7 (all s, CH_2), 14.1 and 13.1 (both s, Me). MS (EI 70 eV): *m*/*z* = 204 [M^+, 12%], 147 [M − Bu, 100%], 129 [M − Bu − H_2O, 79%], 91 [$C_7H_7^+$, 59%].

Preparation of *trans*-3-methyl-4-phenylbut-3-en-2-ol. This compound was prepared as a colorless oil following a similar procedure using *trans*-α-methylcinnamaldehyde (3 mL, 21.5 mmol) and MeLi (1.6 M in diethyl ether, 15 mL, 24 mmol). Yield: 3.011 g (86%). Spectroscopic data were in accordance with those previously reported.[17]

Typical Procedure for Catalytic Isomerization of Allylic Alcohols. Under an inert atmosphere, the ruthenium catalyst precursor (0.04 mmol, 1 mol %), 20 mL of THF, potassium *tert*-butoxide (0.2 mmol, 5 mol %), and the allylic alcohol (4 mmol) were introduced into a Schlenk tube fitted with a condenser. Then, the mixture was heated at the indicated temperature. The reaction

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(8) Note that some other catalytic systems are also able to isomerize trisubstituted allylic alcohols, although they require higher temperatures (from 70 to 120 °C) and/or longer reaction times. See for example ref 2d and: (a) Bricout, H.; Monflier, E.; Carpentier, J.-F.; Mortreux, A. *Eur. J. Inorg. Chem.* **1998**, 1739. (b) Uma, R.; Davies, M. K.; Crévisy, C.; Grée, R. *Eur. J. Org. Chem.* **2001**, 3141. (c) Doppiu, A.; Salzer, A. *Eur. J. Inorg. Chem.* **2004**, 2244. (d) Ganchegui, B.; Bouquillon, S.; Hénin, F.; Muzart, J. *J. Mol. Catal. A: Chem.* **2004**, *214*, 65.

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was monitored by GC and GC/MSD each 5 min during the first hour and then the interval time was increased progressively.

Isomerization of 1-Octen-3-ol with the Catalyst 1c Generated in Situ. Under an inert atmosphere, a solution of [{RuCl(μ-Cl)-(η^6-*p*-cymene)}$_2$] (12.2 mg, 0.020 mmol, 0.040 mmol of Ru) and triethyl phosphite (7.5 μL, 0.044 mmol) in 5 mL of THF was stirred at room temperature for 10 min. Then, potassium *tert*-butoxide (0.2 mmol), 1-octen-3-ol (4 mmol), and 15 mL of THF were added, and the mixture was heated at 35 °C. The inert atmosphere is only required during the catalytic experiment; the formation of the complex can be carried out in the presence of air.

Isomerization of 4-Phenylbut-3-en-2-ol into 4-Phenylbutan-2-one under Preparative Conditions. Under nitrogen atmosphere, 4-phenylbut-3-en-2-ol (2.96 g, 20 mmol), **1c** (0.472 g, 1 mmol), potassium *tert*-butoxide (0.59 g, 5 mmol), and 100 mL of THF were introduced in a Schlenk flask, and the reaction mixture was stirred at 35 °C for 20 min (quantitative conversion by GC). Then, a saturated aqueous solution of NH_4Cl was added. The product was extracted with Et_2O and dried over $MgSO_4$, and the solvents were evaporated. The purification by column chromatography over silica gel, using a mixture of hexane/ethyl acetate (5:1), afforded 4-phenylbutan-2-one as a colorless oil. Yield: 2.43 g (82%).

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