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Efficient transformation of propargylic alcohols to α,β-unsaturated aldehydes catalyzed by ruthenium/water under neutral conditions

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Abstract—α,β-Unsaturated aldehydes were selectively obtained in high yields from propargylic alcohols in aqueous solutions using $RuCpCl(PR_3)_2$ ($Cp=\eta^5$-C_5H_5) as a catalyst. Of the *tert*-phosphine ligands examined, PMe_3 gave the most satisfactory results. Typically, $RuCpCl(PMe_3)_2$ (5 mol%) catalyzed the transformation of oct-1-yn-3-ol at 100°C to give 2-octenal in an isolated yield of 85% ($E/Z=80/20$).

1. Introduction

The Meyer–Schuster-[1] and Rupe-type[2] rearrangements of propargylic alcohols to α,β-unsaturated ketones and aldehydes, which are versatile organic intermediates in the manufacture of natural products of biological or pharmaceutical importance,[3] have been the subject of a large number of investigations. Such transformation is achieved by carrying out the reaction in acidic medium or by using strong acid as a catalyst,[4] which often gives rise to unselective regioproducts. The reaction can be better catalyzed by a variety of transition metal oxides, such as Ti(IV)/CuCl/organic acid,[5] oxovanadium,[6] and Bu_4NReO_4/*p*-TsOH.[7] However, these systems need elevated reaction temperatures and/or acidic conditions. In 1996, the rearrangement reaction was reported to proceed at 100°C under neutral conditions using MoO_2(acac)/dibutylsulfoxide, but could be applied only to tertiary propargylic alcohols since the use of secondary alcohols results in simple oxidation of the alcohol unit.[8] Such oxo-metal complex-catalyzed isomerization has been believed to take place via a [3,3]-sigmatropic rearrangement of the oxo-propargylox–metal intermediate. More recently, a completely different route has been developed by Dixneuf and co-workers to obtain α,β-unsaturated aldehydes: the formal isomerization of HC≡C-C(R)(R′)OH to OHC-CH=C(R)(R′) was achieved at 50–100°C by a two-step but one-pot reaction via ruthenium(II)-catalyzed anti-Markovnikov addition of benzoic acid to the alkyne moiety and subsequent acid-catalyzed cleavage of the resulting enol esters (Eq. (1)).[9] Although one equiv. of benzoic acid is required, this route provides easy access to α,β-unsaturated aldehydes, where the presumed key step is the attack of the α-carbon of the Ru–vinylidene intermediate by PhCOO(−) anion. We previously reported the highly regioselective, efficient, and substituent-tolerant anti-Markovnikov hydration of terminal alkynes to give *n*-aldehyde using a catalytic amount of readily available cyclopentadienylruthenium complexes bearing appropriate bidentate or monodentate phosphine ligands.[10] We report here a reaction system that yields directly and selectively α,β-unsaturated aldehydes when propargylic alcohols (HC≡C-CH(R)OH) are treated with water/alcohol under neutral conditions in the presence of ruthenium catalyst (Eq. (2)). Since benzoic acid/Ru-assisted rearrangement has only been reported for *tert* propargylic alcohols while our water/Ru-assisted reaction is best suited for *sec*-alcohols, the two systems appear complementary.

2. Results and discussion

The reaction of but-1-yn-3-ol (**1a**) in 2-propanol/H_2O at 100°C for 12 h in the presence of 5 mol% of $RuCpCl(PMe_3)_2$ ($Cp=\eta^5$-cyclopentadienyl)[11] led to complete conversion of the starting material with the selective formation of 2-butenal (**2a**) in 96% yield

Keywords: hydration; propargylic alcohol; aldehyde; ruthenium catalyst.

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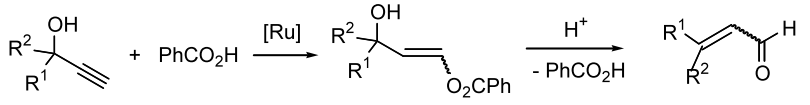
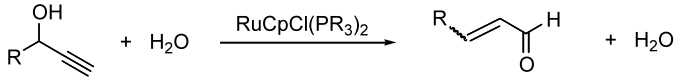
(Table 1, entry 1). Reducing the amount of catalyst to 2 mol% did not lower the yield of **2a**, but a longer reaction time was necessary (entry 3). The addition of NH_4PF_6 or an elevated temperature did not improve the activity of the catalyst. With respect to the phosphine ligand, $RuCpCl(PMe_3)_2$ gave the highest activity: RuCpCl(dppm) (dppm = bis(diphenyl-phosphino)-methane), which was the best catalyst for anti-Markovnikov hydration of various terminal alkynes examined previously, lowered the reaction rate (68%) under the same conditions, probably due to greater steric hindrance (entry 2). Similarly, $RuCpCl(PMe_2Ph)_2$ gave **2a** in only 25% yield while other cyclopentadienylruthenium complexes with different phosphine ligands, $RuCpCl(L)_2$ ($L = PMePh_2$ and PPh_3, $(L)_2 = Me_2PCH_2PMe_2$, $Et_2PCH_2CH_2PEt_2$, and $Ph_2P(CH_2)_nPPh_2$ ($n = 2$–4)), were not effective and resulted in poor yields (0–5%) of **2a**, thus demonstrating the importance of the choice of phosphine ligands in the present catalytic reactions.

Using $RuCpCl(PMe_3)_2$ as a catalyst, the scope of the present transformation reaction of propargylic alcohol derivatives was examined (Table 1, entries 4–8). Pent-1-yn-3-ol (**1b**) was converted to **2b** in 94% yield (entry 4). Likewise, other alkyl-substituted propargylic alcohols **1c**–**e** gave the corresponding α,β-unsaturated aldehydes **2c**–**e** in high yields under similar reaction conditions and the (*E*)-forms were always obtained as the major stereoisomer (entries 5–7). Cinnamyl aldehyde (**2f**) was

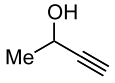
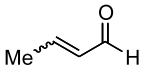
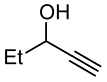
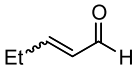
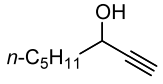
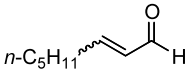
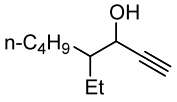
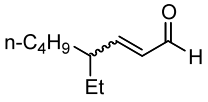
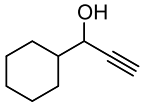
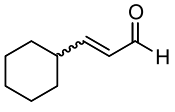
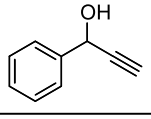
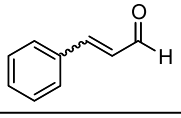


(1)



(2)

Table 1. Formal isomerization of propargylic alcohols catalyzed by ruthenium complexes[a]

Entry	Substrate		Product		Yield, %[b]
1		**1a**		**2a**	96
2[c]					68
3[d]					95
4		**1b**		**2b**	94
5		**1c**		**2c**	93 (85, E/Z = 80/20)
6		**1d**		**2d**	88 (79, E/Z = 84/16)
7		**1e**		**2e**	94 (82, E/Z = 93/7)
8[e]		**1f**		**2f**	(75, E/Z = 94/6)

[a] Propargyl alcohol (1.0 mmol), $RuCpCl(PMe_3)_2$ (0.050 mmol, 5.0 mol %), H_2O (0.75 mL), and *i*- PrOH (2.5 mL) were stirred in a sealed tube at 100 °C for 12 h.

[b] GC yield (isolated yield in parenthesis). When the aldehyde was isolated, the E/Z ratio was determined by ^1H NMR. GC of **2a**-**2c** did not resolve the isomer peaks.

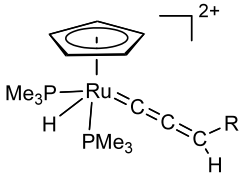
[c] RuCpCl(dppm) was used instead of $RuCpCl(PMe_3)_2$.

[d] The alkyne (5.0 mmol), $RuCpCl(PMe_3)_2$ (0.10 mmol, 2.0 mol %), H_2O (1.5 mL), and *i*-PrOH (5.0 mL) were stirred in a sealed tube at 100 °C for 24 h.

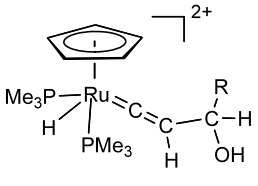
[e] Reaction time, 60 h.

formed from 3-phenyl-prop-1-yn-3-ol (**1f**), again with the *E* isomer as the predominant form, but the reaction was slow and a longer reaction time (60 h) was required (entry 8). Tertiary propargylic alcohols, 3-methyl-but-1-yn-3-ol, and 3-phenyl-but-1-yn-3-ol, were scarcely transformed to α,β-unsaturated aldehydes, and remained unreacted under these conditions: elevated reaction temperatures (e.g. 140°C) caused formation of side products.

The reaction is formally a 1,3-shift isomerization of the hydroxy group, but does not proceed without the presence of adequate water. To confirm that the present process does not involve the concerted 1,3-migration of the alcoholic OH group, the reaction of **1c** was carried out in a mixture of $H_2{}^{18}O$ and 2-propanol. The obtained aldehyde exclusively contained ^{18}O, *n*-$C_5H_{11}CH{=}CHC(={}^{18}O)H$ (**2c**–^{18}O), as was obvious by the red-shift of the stretching vibration of the carbonyl group compared to that of **2c** [*n*(CO): 1695 cm^{-1} in **2c**, 1662 cm^{-1} in **2c**–^{18}O]. Therefore, it is obvious that the net reaction is anti-Markovnikov hydration at the terminal alkyne carbon with concomitant dehydration of the original OH group. The established reaction mechanism for the previously reported anti-Markovnikov hydration of 1-alkynes[12] may be applied to the present hydration of propargylic alcohols, although it is not yet clear when the dehydration takes place. Early-stage dehydration should give Ru–allenylidene intermediate (**A**) followed by nucleophilic attack of the α-carbon of the allenylidene unit by OH(–): the ability of Ru–allenylidene complexes to react with weak nucleophiles, such as alcohol and amine, at C(α) has been reported.[13] Alternatively, the dehydration could occur after the attack of C(α) of γ-hydroxyvinylidene intermediate (**B**) by water and successive formation of a γ-hydroxyacyl complex. In any case, the key-intermediate should have a Ru(IV) metal center which bears a hydride and an allenylidene (or (hydroxy)vinylidene) units. Interestingly, Bassetti and co-workers very recently applied the anti-Markovnikov hydration of 1-alkynes to propargylic alcohols in micellar solutions at 60°C and obtained saturated β-hydroxyaldehydes.[14]



(**A**)



(**B**)

In summary, we have found a highly selective transformation of propargylic alcohols to α,β-unsaturated aldehydes in high yields in the presence of water and a catalytic amount of ruthenium complex. This reaction is remarkably clean and proceeds under neutral conditions. In general, the reaction mixture simply consists of solvent, water, unreacted reactants, and the α,β-unsaturated aldehydes formed regardless of the conversion, while few if any by-products are detected throughout the reaction. Further applications of this reaction, as well as detailed mechanistic investigations, are now in progress.

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