Ruthenium-Catalyzed Addition Reaction of Alcohols across Olefins

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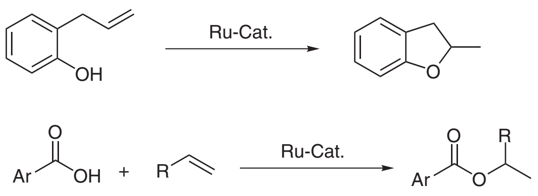
Abstract: 2-Phenylethanol was added to olefins catalyzed by ruthenium catalytic system Cp*RuCl$_2$(PPh$_3$)/2AgOTf in toluene. This reaction proceeded without β-hydride elimination, giving saturated ethers in good yields.

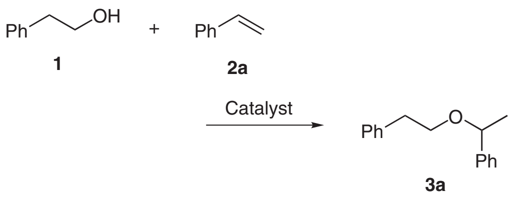
Key words: addition reactions, ruthenium, alcohols, alkenes, ethers

Synthetic organic reactions catalyzed by transition metal complexes have enormously progressed for the last 2 decades. Highly regio- and stereoselective synthetic methodologies thus developed have been made possible syntheses of complicated natural products and pharmaceutical active compound as well as functional molecules. Addition reactions, which include the transition metal-catalyzed hydrosilylation,[1] hydroboration,[2] hydroalumination, hydroamination[3] and so on, have found wide synthetic applications. Furthermore, addition reactions of oxygen nucleophiles to olefins by use of Brønsted acids, stoichiometric amount of Lewis acid[4] and mercuric salts[5] have been known and utilized.

Wacker reaction catalyzed by palladium salt also involves the addition of oxygen nucleophiles to olefins, ending up with accompanying β-elimination to give unsaturated compounds.[6] Herein, we wish to report new ruthenium-catalyzed addition reactions of oxygen nucleophiles to olefins affording saturated adducts. Two examples of ruthenium-catalyzed intramolecular[7] and intermolecular[8] addition reactions of 2-allylphenol and benzoic acid derivatives produced selectively 2-methyl benzofuran and benzoate derivatives, respectively, in moderate to good yields (Scheme 1). It is noted that no unsaturated product, which may be derived from accompanying β-hydride elimination, was detected. It is also remarked that the present addition reactions proceed with complete regioselectivity according to Markovnikov's rule. Some results of intermolecular 'hydroalkoxylation' of styrene with 2-phenylethanol catalyzed by Ru(III) complexes are summarized (Scheme 2, Table 1).



Scheme 1



Scheme 2

When (Cp*RuCl$_2$)$_2$ was used as a catalyst precursor in the absence of AgOTf, no reaction took place (entry 1). Cationic ruthenium complex activated by AgOTf promoted the addition reaction of **1** with **2a** (entry 2), and addition of triphenylphosphine (PPh$_3$) on the ruthenium complex catalyst increased the catalytic activities (entry 4). However, the activities of the cationic ruthenium complexes were improved significantly by use of neither electron poor phosphine ligand (2-Fur$_3$P) nor electron rich phosphine ligand (CyPh$_2$P) (entries 6, 7). Employment of bidentate phosphine ligand (dppb) also did not cause improvement of chemical yield (entry 5). So far, PPh$_3$ was the best choice of a ligand in this reaction. When Cp*RuCl$_2$(Ph$_3$P), prepared independently,[9] was used as a catalyst precursor, the yield was slightly increased with a saving of AgOTf (entry 9).

With the best catalyst Cp*RuCl$_2$(Ph$_3$P)/AgOTf in hand, the 'hydroalkoxylation' reactions were optimized (entries 8–12). When the hydroalkoxylation reaction was carried out by stirring a mixture of an excess of 2-phenylethanol substrate with styrene in the presence of 2 mol% of the ruthenium complex catalyst at reaction temperature of 85 °C, the hydroalkoxylation reaction afforded the corresponding ether product in 49% yield (entry 8). The higher reaction temperature may have resulted in competitive oligomerization of styrene. On the other hand, use of an excess of styrene at reaction temperature as high as 70 °C provided a satisfactory product yield (83% yield, entry 12).

Hydroalkoxylation of **1** with some other olefins in the presence of cationic ruthenium catalyst Cp*RuCl$_2$(Ph$_3$P)/2AgOTf are shown in Table 2.

A simple terminal olefin, 1-octene (**2b**) was reacted with **1** in the presence of 10 mol% of ruthenium catalyst at 100 °C to give the corresponding ether **3b** in 66% yield.

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Table 1 Effects of Catalyst, Temperature and Molecular Ratio on the Hydroalkoxylation Reaction of 2-Phenylethanol (**1**) with Styrene (**2a**)[a]

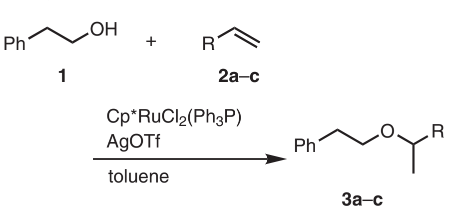
Entry	Ruthenium complex (mol%)	Ligand	Silver salt (mol%)	Temp (°C)	Ratio **1**:**2a**	Yield (%)[b]
1	$(Cp^*RuCl_2)_2$ (1)	None	None	85	1:1	0
2	$(Cp^*RuCl_2)_2$ (1)	None	AgOTf (6)	85	1:1	33
3	$(Cp^*RuCl_2)_2$ (1)	Ph_3P	$AgBF_4$ (6)	85	1:1	16
4	$(Cp^*RuCl_2)_2$ (1)	Ph_3P	AgOTf (6)	85	1:1	54
5	$(Cp^*RuCl_2)_2$ (1)	DPPB	AgOTf (6)	85	1:1	44
6	$(Cp^*RuCl_2)_2$ (1)	$(2\text{-Fur})_3P$	AgOTf (6)	85	1:1	41
7	$(Cp^*RuCl_2)_2$ (1)	$CyPh_2P$	AgOTf (6)	85	1:1	47
8	$Cp^*RuCl_2(Ph_3P)$ (2)	None	AgOTf (4)	85	2:1	49
9	$Cp^*RuCl_2(Ph_3P)$ (2)	None	AgOTf (4)	85	1:1	56
10	$Cp^*RuCl_2(Ph_3P)$ (2)	None	AgOTf (4)	85	1:2.5	72
11	$Cp^*RuCl_2(Ph_3P)$ (2)	None	AgOTf (4)	100	1:2.5	38
12	$Cp^*RuCl_2(Ph_3P)$ (2)	None	AgOTf (4)	70	1:2.5	83

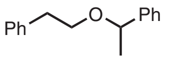
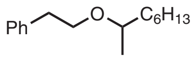
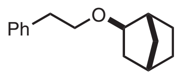
[a] Reaction conditions: 2-Phenylethanol (1 mmol), styrene and Ru/Ag/Ligand were stirred in toluene (2 mL).

[b] Isolated yield after the purification by silica gel column chromatography. Yields were based on 2-phenylethanol except entry 7.

Strained 2-norbornene (**2c**) was subjected to the hydroalkoxylation with 2-phenylethanol in a 1:1 molar ratio at 85 °C to afford 2-phenylethyl *exo*-2-norbornyl ether (**3c**) in an excellent yield. Attempts for hydroalkoxylation reactions with secondary and tertiary alcohols all failed.

Table 2 Ruthenium-Catalyzed Hydroalkoxylation Reactions of 2-Phenylethanol with Olefins (**2a–c**)[a]



Entry	Olefin (equiv)	Product	Yield (%)[b]
1	Styrene (**2a**) (2.5)	 **3a**	83
2[c]	1-Octene (**2b**) (10)	 **3b**	66
3	2-Norbornene (**2c**) (1)	 **3c**	89

[a] Reaction conditions: 2-phenylethanol (1 mmol), olefin and $Cp^*RuCl_2(Ph_3P)/2AgOTf$ (0.2 mmol) were stirred in toluene, at 70 °C, for 48 h.

[b] Isolated yield after the purification by silica gel column chromatography.

[c] Reaction was carried in the presence of 10 mol% Ru at 100 °C.

Presumably, the hydroalkoxylation reaction starts with the coordination of olefin substrate to the ruthenium complex, followed by nucleophilic attack of the alcohol for the resultant activated olefin. Accordingly, the hydroalkoxylation remarkably depended upon a molar ratio of olefin and alcohol, i.e., an excess amount of olefin substrate favored the hydroalkoxylation, while an excess of alcohol retarded the reaction. The regioselectivite Markovnikov addition of the hydroalkoxylation reaction may suggest a carbonium ion character of the intermediate generated from olefin coordination on ruthenium complex.

In conclusion, we found that cationic ruthenium catalyst $CpRuCl_2(Ph_3P)/2AgOTf$ promoted the addition reaction of primary alcohol to olefins. Further studies including to clarifying the mechanistic aspects on hydroalkoxylation are now going.

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(10) **Typical Procedure of Ruthenium-Catalyzed Hydroalkoxylation Reaction of 2-Phenylethanol(1) with Styrene (2a) Described in Table 2, Entry 1.**
$Cp^*RuCl_2(Ph_3P)$ (11 mg, 0.02 mmol) was dissolved in toluene (2 mL) and the solution was heated to 85 °C. After 15 min, AgOTf (11.5 mg, 0.045 mmol) was added and stirred at 85 °C for 3 h. The reaction mixture was cooled to r.t. 2-Phenylethanol (**1**, 122 mg, 1.0 mmol) and styrene (**2a**, 260 mg, 2.5 mmol) were added. The reaction mixture was heated to 70 °C and stirred for 48 h. The crude product was purified by silica gel chromatography (hexane–EtOAc = 10:1), yielding product **3a** (187 mg, 83%).