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A Formal anti-Markovnikov Hydroalkoxylation of Allylic Alcohols with a Ruthenium Catalyst

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A Formal anti-Markovnikov Hydroalkoxylation of Allylic Alcohols with a Ruthenium Catalyst

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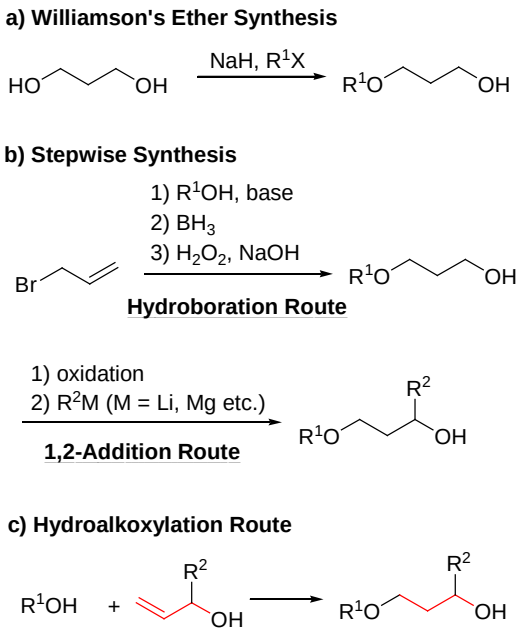
Hydroalkoxylation of C-C double bonds was achieved through the use of a ruthenium catalyst. The reaction of allylic alcohols with nucleophilic alcohols was carried out in the presence of a ruthenium catalyst prepared by RuClH(CO)(PPh3)3 and 2,6-bis(n-butyliminomethyl)-4-(piperidin-1-yl)pyridine under mild reaction conditions to afford the corresponding γ–alkoxypropanols in good yield.

Keywords: Hydroalkoxylation, Allylic Alcohols, Ruthenium Catalyst

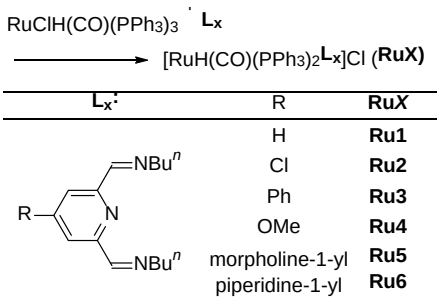
γ–Alkoxypropanol and its derivatives are frequently used as starting materials or intermediates for the synthesis of macrocyclic compounds, polyethers, dendrimers, and other bioactive compounds.[1-3] Monoalkylation of 1,3-propanediol with alkyl halide in the presence of a strong base, the so-called Williamson ether synthesis, is the most commonly used method for the synthesis of this class of compounds (Scheme 1, a).[1] It is known that alkylation of allylic alcohols followed by hydroboration/oxidation also affords the corresponding 3-alkoxypropanols (Scheme 1, b).[2] Optically active α-alkyl or α-aryl-γ-alkoxypropanols are often synthesized by oxidation of 3-alkoxypropan-1-ols generated by the reactions described above and 1,2-addition of organometallic reagents onto the resulting aldehydes.[3] It is considered that hydroalkoxylation of carbon-carbon double bonds of allylic alcohols is one of the most straightforward and environmentally benign pathways to this class of compound because of its high atom efficiency, though it is highly scarce (Scheme 1, c). Yamakawa and co-workers reported a reaction of allyl alcohol with methanol using an MgO catalyst to form 3-methoxypropan-1-ol, though the conversion of allyl alcohol was of a low percentage (< 30%) and only one combination of substrates was tested.[4] The other methods met with problems such as homo-hydroalkoxylation of allyl alcohol and low conversion percentages and selectivities.[5]

On the other hand, we have recently reported a novel formal *anti*-Markovnikov hydroamination of allylic alcohols via a tandem oxidation/1,4-addition/reduction based on the "borrowing hydrogen" method.[6] Of note is that the expected side-reactions such as isomerization of π-bonds[7], decomposition of allylic aclohols by redox reactions[8], and aldol-type reactions[9] are suppressed. We considered that γ-alkoxypropanols would be synthesized under mild reaction conditions, if our catalysis worked well in the reaction of allylic alcohols with nucleophilic alcohols. We propose here a synthetic method for γ-alkoxyalcohols through ruthenium-catalyzed "borrowing hydrogen"-based formal *anti*-Markovnikov hydroalkoxylation of allylic alcohols.

The ruthenium catalyst was in situ generated from $RuClH(CO)(PPh_3)_3$, which is frequently used for hydrogen



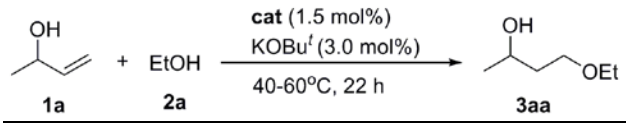
Scheme 1 Synthetic routes for γ-alkoxypropanols.



Scheme 2 Preparation of ruthenium complexes **Ru1-6**.

transfer-related reactions,[6f,10] with 2,6-bis(n-butylimino-methyl)pyridine (**L1**) by our previously reported hydroamination. In the course of our research, we found that a cationic ruthenium complex $[RuH(CO)(PPh_3)_2(\mathbf{L1})]Cl$ **Ru1** was obtained by the reaction of $RuClH(CO)(PPh_3)_3$ with **L1** in $CHCl_3$ at room temperature overnight in 87% yield (Scheme 2). This complex was determined by ^1H and ^{31}P NMR and FAB-MS (HRMS) spectra, suggesting that **L1** acts as a $N_{pyridine}$,N_{imine}-bidentate ligand in the present complex. We also found that the obtained ruthenium complex **Ru1** shows better catalytic activity than the in situ generated catalyst. Thus, the reaction of morpholine with 3-buten-2-ol was carried out in the presence of 1.5 mol % of **Ru1** to give the corresponding γ–aminoalcohol in 99% yield,

Table 1 Optimization of reaction conditions[a]



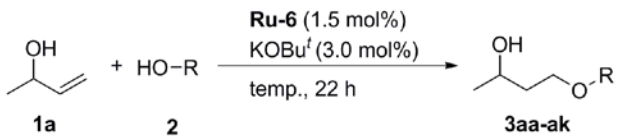
entry	cat	Yield of **3aa** (%)[b]			
		30°C	40°C	50°C	60°C
1	**Ru1**	15	48	39	34
2	**Ru2**	-	3	58	54
3	**Ru3**	17	46	51	39
4	**Ru4**	57	65	53	53
5	**Ru5**	53	71	60	50
6	**Ru6**	61	76 (66)[c]	-	43

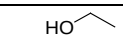
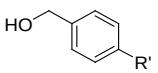
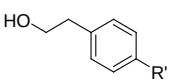
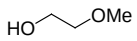
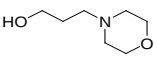
[a]Reaction conditons: catalyst (0.03 mmol), KOBu^t (0.06 mmol), 3-buten-2-ol (**1a**) (2.0 mmol), and ethanol (**2a**) (8.6 mmol, 0.5 mL), for 22 h. [b]Determined by ^{1}H NMR. [c]The value in parentheses is isolated yield.

whereas the same reaction with 2 mol % of $RuHCl(CO)(PPh_3)_3$ and 2.2 mol % of **L1** obtained a 76% yield of product. Therefore, the catalytic reactions in this study were performed using the prepared catalyst **Ru1-6** prior to the catalytic reaction.

A series of these ruthenium complexes **Ru1-6** was synthesized and used to test the catalytic efficiency on the present hydroalkoxylation (Table 1). The reaction of ethanol (**2a**) with 3-buten-2-ol (**1a**) was carried out in the presence of KOBut and ruthenium catalyst **Ru1** at 60°C to afford 4-ethoxy-2-butanol (**3aa**) in 34% yield (entry 1 at 60°C, Table 1). To improve the reaction efficiency, we investigated the reaction temperature and various ruthenium catalysts bearing several types of substituents at the *C*4-position of the pyridine rings (entries 2-6). In the presence of **Ru1**, the reaction at 40°C provided **3aa** in 48% yield. For both the **Ru2** and **Ru3** catalysts, which have electron withdrawing chlorine atom and phenyl group on the 4-position of the pyridine ring, the reaction at 40°C was apparently slower than that with **Ru1**, whereas an increase in chemical yield was observed at 50°C (58% and 51% yield, entries 2 and 3). Installing the electron donating methoxy group on the ligand improved the catalytic activity so as to afford **3aa** in 65% yield even at 40°C (entry 4). Cyclic and secondary amino groups, which are stronger electron donating groups than the methoxy group, had more influence than **Ru4** did (entries 5 and 6) and **Ru6** showed the highest catalytic activity among **Ru1-6** and provided a satisfactory 76% yield of **3aa** at 40°C. ^{1}H NMR analysis of the crude products suggested that the causes of decreases of chemical yields at the lower temperature were different from that at the higher temperature. Thus, the starting alcohol **2a** was almost consumed at the higher temperature to afford several by-products such as 2-butanone and 2-butanol, though **2a** was recovered at the lower reaction temperature after the reaction. Hydroalkoxylation reactions of several

Table 2 Reaction products of **1a** with **2a-k** in the presence of **Ru6**[a]

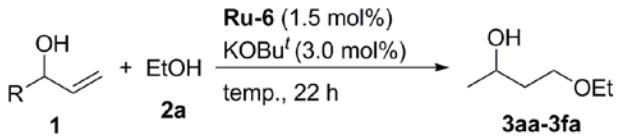


entry	HO-R	product	temp. (°C)	Yield (%)[b]
1	 **2a**	**3aa**	40	76 (66)
2	 R' = H (**2b**)	**3ab**	50	69 (44)
3	R' = OMe (**2c**)	**3ac**	50	78 (41)
4	R' = Cl (**2d**)	**3ad**	50	26
5[c]	R' = Cl (**2d**)	**3ad**	50	46 (33)
6[d]	R' = Br (**2e**)	**3ae**	50	7
7	 R' = H (**2f**)	**3af**	40	62 (35)
8	R' = OMe (**2g**)	**3ag**	50	70 (41)
9	R' = Cl (**2h**)	**3ah**	60	61 (33)
10	 **2i**	**3al**	40	64 (27)
11	 **2j**	**3aj**	60	31 (9)
12	 **2k**	**3ak**	50	13 (5)

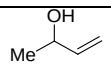
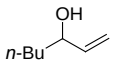
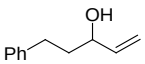
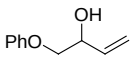
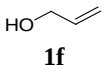
[a]Reaction conditions: **Ru6** (0.03 mmol), KOBu^t (0.06 mmol), 3-buten-2-ol (**1a**) (2.0 mmol), and alcohol (8.6 mmol), for 22 h. [b]Determined by ^{1}H NMR, and values in parentheses are isolated yields. [c]**1a** (0.5 mL), and **2d** (2 mmol) was used. [d]Toluene (0.5 mL) was added.

nucleophilic alcohols **2a-k** with 3-buten-2-ol (**1a**) were examined under optimized catalytic conditions (Table 2). In some cases, the isolated yields were much lower than that determined by ^{1}H NMR. In these cases, it is difficult to separate the desired products from the starting materials and/or by-products, such as saturated alcohols and/or ketones generated by disproportionation of allylic alcohols, and the ethers generated by undesired hydroalkoxylation between two molecules of allylic alcohols, by silica gel column chromatography and then by recycle gel permeation chromatography.

Table 3 Reaction products of **2a** with **1a-k** in the presence of **Ru6**[a]

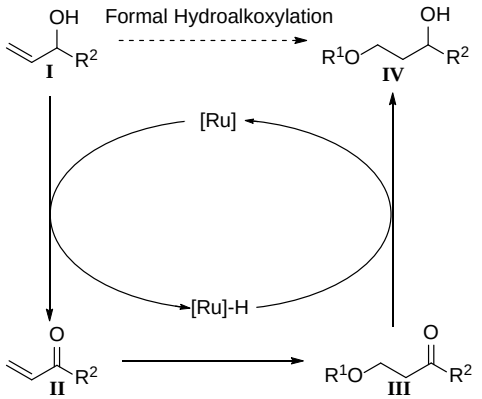


1 3aa-3fa

entry	Allylic alcohol	product	temp. (°C)	Yield (%)[b]
1	 **1a**	**3aa**	40	76 (66)
2	 **1b**	**3ba**	60	58 (47)
3	 **1c**	**3ca**	50	65 (42)
4	 **1d**	**3da**	50	33 (12)
5	 **1e**	**3ea**	50	55 (33)
6[c]	 **1f**	**3fa**	70	56 (21)
7[d]	**1f**	**3fb**	70	48 (39)

[a]Reaction conditions: **Ru6** (0.03 mmol), KOBu^t (0.06 mmol), allylic alcohol (2.0 mmol), and **2a** (8.6 mmol, 0.5 mL), for 22 h. [b]Determined by ^{1}H NMR, values in parentheses are isolated yields. [c]EtOH (19.2 mmol, 1 mL) was used. [d]Benzyl alcohol (**2b**) (8.6 mmol) was used instead of **2a**.

Treatment of benzyl alcohol (**2b**) and 4-methoxybenzyl alcohol (**2c**) with **1a** in the presence of the **Ru6** catalyst at 50°C afforded the corresponding γ-alkoxy-1-propanols **3ab** and **3ac** in 69% and 78% yield, respectively (entries 2 and 3). Reaction with 4-chlorobenzyl alcohol (**2d**) afforded the ether in 26% yield, but the reaction with 4-bromobenzyl alcohol (**2e**) failed to give the corresponding ether (only 7% yield, entries 4 and 6). The product yield of **3ad** improved when excess **1a** was used (entry 5). It was found that 2-arylethanols **2f-h** reacted nicely with **1a** under similar mild reaction conditions to give the corresponding products **3af-3ag** in good yields (entries 7-9). Ethylene glycol monomethyl ether (**2i**) was tolerated in the present ether synthesis to obtain the corresponding methoxyethylene ether **3ai** in 64% yield (entry 10). A γ-amino alcohol **2j**, which is one of the reaction products obtained through hydroamination of allylic alcohol that we previously reported, gave the alkoxy alcohol **3aj** having a heterocyclic ring in 31% yield (entry 11). Compared with the primary



Scheme 3 Possible reaction mechanism

alcohols, the secondary alcohol showed lower reactivity, giving isopropyl ether in only 13% yield accompanied with apparent disproportionation of **1a** (entry 12), presumably due to the steric hindrance of the nucleophilic alcohol.

Table 3 shows reaction products of ethanol (**2a**) with several types of allylic alcohols **1a-f**. Allylic alcohols 1a-c bearing aliphatic substituents at the α-carbon showed good reactivity, giving the corresponding γ-ethoxy alcohol **3aa-3ca** in 58-76% yield (entries 1-3). On the other hand, α-phenylallyl alcohol (**1d**) showed lower reactivity, giving **3da** in 33% yield (entry 4). In this case, the oligomerization of the starting alcohol **1d** was observed on the ^{1}H NMR spectrum of the crude product. 1-Phenoxy-3-buten-2-ol (**1e**) was acceptable for the reaction substrate to afford the corresponding alcohol **3ea** in good yield (entry 5). The simplest substrate, allyl alcohol (**1f**), also showed good reactivity, providing a 56% yield of 3-ethoxypropan-1-ol (**3fa**) (entry 6). The reaction of benzyl alcohol (**2b**) with allyl alcohol (**1f**) also proceeded nicely to give 1,3-propylene glycol monobenzyl ether (**3fb**) in 48% yield (entry 7), which is often used as a starting material in the total synthesis of macrocyles.[1-3] It is noteworthy that the desired cross hydroalkoxylation took place selectively; nevertheless, the allyl alcohol (**1f**) and nucleophilic alcohols **2a** and **2b** are both primary alcohols in the case of entries 6 and 7.

It is considered that the reaction proceeds through the "borrowing hydrogen" process (Scheme 3).[11] Thus, the β-hydride elimination of ruthenium alkoxide species generated by allylic alcohol **I** and ruthenium complex forms the corresponding α,β-unsaturated carbonyl intermediate **II** and a Ru-H species. Nucleophilic alcohol attaches to the β-carbon to form the β-alkoxy ketone **III**, to which the "borrowed" hydrogen is returned to afford the desired γ-alkoxypropanols **IV**. Nucleophilic attack of allylic alcohol **I** to the intermediate **II** leads the formation of undesired γ-allyloxypropan-1-ol derivatives. To avoid this side reaction, use of excess amount of the nucleophilic alcohol is required. The same result should be obtained even by using the corresponding α,β-unsaturated carbonyl compound **II** as a starting material, since an excess amount of nucleophilic alcohol would work as a hydrogen source. However, no desired product **3aa** was afforded when the reaction of

methyl vinyl ketone (MVK) with ethanol **2a** was performed under the optimized reaction conditions at 40ºC (same as entry 6 in Table 1), and ^{1}H NMR analysis of the crude product implied that the polymerization of MVK mainly proceeded. Therefore, we considered that generation of appropriate amount of α,β-unsaturated carbonyl intermediate **II** through the borrowing hydrogen process is important for the successful formation of the corresponding γ-alkoxy alcohols **IV**, in which consumption of reactive intermediate **II** by polymerization would be suppressed.

In summary, a ruthenium catalysis for the hydroalkoxylation of allylic alcohols was developed. The reaction tolerated several combinations of allylic alcohols including methoxyethanol and amino alcohols and provided the corresponding γ-alkoxypropanols in good yield under mild reaction conditions.

Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

References and Notes

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