Catalytic Oxidation of α-Carbon of Ethers Utilizing Binuclear Copper(II) Complex of 7-Azaindole

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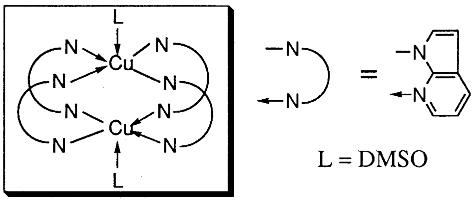
Treatment of benzyl ethyl ether with a catalytic amount of binuclear copper(II) complex of 7-azaindole **1** under oxygen atmosphere at 80 °C produced ethyl benzoate in 10400% yield based on the catalyst. This reaction could be also applied to other ethers (e.g., alkyl benzyl ethers and dialkyl ethers) to give α-oxygenated products catalytically.

In recent years, binuclear complexes containing copper have been drawing much attention in biochemistry.[1] For example, binuclear copper complexes in hemocyanin and tyrosinase play important roles in oxygen transport and oxidation in organisms. While the behavior of this type of complexes toward oxygen have been reported on related mimics for copper dependent monooxygenases,[2] application of the complexes to organic synthesis has rarely been known.[1] As a ligand which would affect electronical properties of metals, we employed 1*H*-pyrrolo[2,3-*b*]pyridine (7-azaindole). The Copper (II) complex **1**[3] has the most attractive structure, where the copper binds to two pyrrole nitrogen atoms and coordinates to two pyridine nitrogen atoms, since the complex may be regarded as a sort of model for porphyrin.



Cu Complex **1**

As chemical functions of binuclear complexes containing 7-azaindole have rarely been known, it is significant to investigate the behavior of the complex **1** under molecular oxygen from the view point not only of biochemistry but also of synthetic organic chemistry. Here we report catalytic oxygenation reaction of several ethers utilizing the complex **1** under molecular oxygen.

The oxygenation of the α-carbon of ethers using metal or metal oxides has been widely studied.[4] For example, metal oxides in higher oxidation states, such as RuO_4,[5] CrO_3,[6] and $KMnO_4$,[7] are among a few stoichiometric oxidants. Whereas, the catalytic oxygenation of ethers to esters with a binuclear copper complex and molecular oxygen has not been reported.

To begin with, benzylic ethers were employed to investigate the oxidation ability of Cu complex **1**. When benzyl ethyl ether (**2b**; 4.08 g, 30 mmol) was treated with **1** (30 mg, 0.04 mmol) for 20 h under oxygen atmosphere at room temperature, ethyl benzoate was obtained in 2800% yield based on Cu(II) along with benzaldehyde in 800% yield (Table 1, run 1). Since this reaction did not occur under argon, the carbonyl oxygen is considered to derive from molecular oxygen. By increasing the reaction time and/or temperature, the yield could be improved (run 3 and 4).

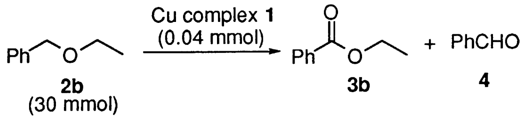


Table 1. Catalytic oxidation of benzyl ethyl ether under various conditions

run	temp. (°C)	time (h)	atmosphere (1 atm)	turnover number[a]	
				3b	**4**
1[8]	rt	20	O_2	28	8
2	rt	20	Ar	0	0
3	rt	100	O_2	46	12
4	80	20	O_2	104	22

[a] determined by ^{1}H-NMR and based on Cu(II).

Copper(II) acetate monohydrate, which exists in a dimeric form similar to Cu complex **1**, was tested as a substitute for the complex **1**. The reaction was carried out by the same procedure as that for run 1 of Table 1 and the results are listed in Table 2.

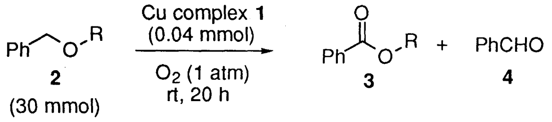
Table 2. Effect of Cu(II) acetate and additives in the oxidatin of benzyl ethyl ether

run	Cu(II) (0.08 mmol)	additive (0.16 mmol)	turnover number[a]	
			3b	**4**
1	$Cu(OAc)_2·H_2O$	——	0	0
2	$Cu(OAc)_2·H_2O$	pyridine	trace	trace
3	$Cu(OAc)_2·H_2O$	2,2'-bipyridyl	2	1
4	$Cu(OAc)_2·H_2O$	7-azaindole	6	3

[a] determined by ^{1}H-NMR and based on Cu(II).

In the case of $Cu(OAc)_2•H_2O$ alone, the starting material was recovered (run 2). Though the oxidation proceeded slightly in the presence of a heterocyclic ligand, the oxidation ability of the acetate was not so good as Cu complex **1**.

To clarify the oxidation mechanism, the effect of alkyl substituent of alkyl benzyl ethers (alkyl : Me, Et, *i*-Pr, or *t*-Bu) was studied at room temperature for 20 h (Table 3). When the substituent was methyl group, the oxidation scarcely proceeded. The yields of esters increased with the increase in the bulkiness of the alkyl substituents (tertiary > secondary > primary). The result implies that the coordination of an ether to the catalyst is not crucial in the oxidation. Thus the ionization potential of the ethers was calculated by MOPAC (AM1 method) and the relationship between the turnover number and calculated ionization potential is depicted in Figure 1. A good correlation is observed between the reactivity and the calculated ionization potential. Namely, the reactivity became higher with the decrease



2
(30 mmol)

3

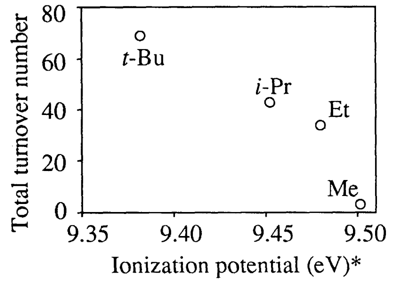
4

Table 3. Effect of alkyl substituent

run	R	turnover number[a]	
		3	**4**
1	Me (**2a**)	2	1
2	Et (**2b**)	28	8
3	*i*-Pr (**2c**)	35	8
4	*t*-Bu (**2d**)	52	17

[a] determined by ^{1}H-NMR and based on Cu(II).

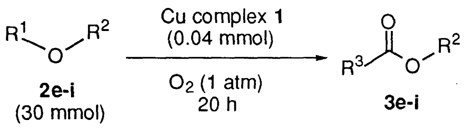
Figure 1. Relationship between turnover number and calculated ionization potential



*calculated by AM1 method.

in the value of ionization potential. It can therefore be presumed that outer sphere electron transfer is the rate-determining step and the reactivity depends on ionization potential of ethers.

The reaction was also applied to dialkyl ethers and the results are summarized in Table 4.



2e-i
(30 mmol)

3e-i

Table 4. Catalytic oxidation of aliphatic ethers with Cu complex **1**

run	R^1	R^2	temp (°C)	R^3	R^2	turnover number[a]
1	*n*-Bu	*n*-Bu	rt	*n*-Pr	*n*-Bu	0 (**3e**)
2	*n*-Bu	*n*-Bu	60	*n*-Pr	*n*-Bu	6 (**3e**)
3	*n*-Bu	*n*-Bu	80	*n*-Pr	*n*-Bu	19 (**3e**)
4	*n*-Bu	Me	80	*n*-Pr	Me	0 (**3f**)
5	$-(CH_2)_3-$		rt	$-CO(CH_2)_2-$		0 (**3g**)
6	$-(CH_2)_4-$		rt	$-CO(CH_2)_3-$		5 (**3h**)
7	$-(CH_2)_5-$		rt	$-CO(CH_2)_4-$		0 (**3i**)

[a] determined by ^{1}H-NMR and based on Cu(II).

Though *n*-butyl ether was not oxidized at room temperature in clear contrast to alkyl benzyl ethers (run 1), butyl butyrate was obtained in 600% yield at 60 °C and in 1900% at 80 °C (run 2, 3). When cyclic ethers (e.g., oxetane, tetrahydrofuran, and tetrahydropyran) were subjected to the reaction, only THF was oxygenated to γ-butyrolactone in 500% yield under mild conditions (run 5, 6, and 7). These results could be explained again by the correlation with calculated ionization potentials.

To clarify the mechanism of these oxidation reaction, the effect of Cu(I) species, which is presumed to generate in the reaction system, was investigated by adding some reductants. On addition of one equivalent of *n*-hexylaldehyde, THF was oxidized exclusively to α-(hydroperoxy)tetrahydrofuran in 4500% yield (at rt, for 20 h) but not to the corresponding lactone. This result will provide the clue for improvement of the oxidation ability and clarification of the reaction mechanism, which are under investigation.

In summary, we could catalytically oxygenate the α-carbon of ethers under molecular oxygen utilizing the binuclear copper(II) complex of 7-azaindole. It is suggested that outer sphere electron transfer is an important factor in this reaction because of being influenced by ionization potential of ethers but not by steric hindrance. Continuing study on the oxidation of other heteroatom compounds is in progress.

References and Notes

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8 Conversion of **2b** was rather low (25%) under the conditions. Other products (e.g. ethanol) could not be detected after workup with sat. NH_4Cl aq., though a small amount of benzyl alcohol was detected in the reaction of dibenzyl ether.