



## Modified Markó's aerobic oxidation of alcohols under atmospheric pressure with air or molecular oxygen at room temperature

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### ABSTRACT

A modified version of Markó's aerobic oxidation procedure, using highly pure (99.995+%) CuCl with 4,7-diphenyl-1,10-phenanthroline (**dpPhen**), DBAD, and Cs<sub>2</sub>CO<sub>3</sub> (98% purity) successfully oxidized primary and secondary alcohols to the corresponding aldehydes and ketones in excellent yield at room temperature with either air or molecular oxygen under atmospheric pressure.

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Oxidation of alcohols to their corresponding aldehydes or ketones is one of the most fundamental reactions in organic chemistry,<sup>1</sup> and numerous useful reagents have been developed. However, many of these agents require stoichiometric quantities, and are toxic or hazardous even after the reactions have been completed.<sup>1</sup>

From an environmental point of view (i.e., green chemistry), catalytic systems using air or molecular oxygen as the ultimate oxidant have drawn much attention.<sup>2–4</sup> Of these systems, copper catalysts are among the most economical and environmentally-acceptable metallic elements<sup>4</sup> and aerobic processes with copper are quite promising. However, these procedures are limited by (i) the requirement for higher temperature (50–90 °C) to obtain better yields, (ii) the low reactivity of secondary and/or non-allylic and -benzylic alcohols, and (iii) the occasional failure of air to oxidize alcohols due to lower reactivity. To overcome these drawbacks, we focused on the Markó's aerobic oxidation<sup>4a–h</sup> and modified it for application in the reactions of a variety of alcohols, even secondary and/or non-allylic and -benzylic alcohols, under atmospheric pressure with air or molecular oxygen at room temperature.

In 1996, Markó and co-workers reported<sup>4a–f</sup> that a newly developed CuCl/**phen**/DBAD-H<sub>2</sub> (or DBAD) complex (see Fig. 1. **phen** = 1,10-phenanthroline, DBAD-H<sub>2</sub> = di-*tert*-butyl hydrazodicarboxylate, and DBAD = di-*tert*-butyl azodicarboxylate) achieved the aerobic oxidation of alcohols in the presence of K<sub>2</sub>CO<sub>3</sub> in toluene under atmospheric pressure of molecular oxygen at 70–90 °C.

After that, his group has continued to improve the copper-catalyzed aerobic oxidation system and their protocol has become one of the most promising processes for the oxidation of a wide variety of alcohols.

Our initial studies followed Markó's primary procedure<sup>4a–f</sup> using DBAD-H<sub>2</sub> for primary alcohols and DBAD for secondary alcohols, and found that the oxidation of undecan-1-ol (**1**) could be achieved after 0.5 h using CuCl freshly prepared by the reaction of CuCl<sub>2</sub> (guaranteed reagent, 98% purity) with Na<sub>2</sub>SO<sub>3</sub> (guaranteed reagent, 98% purity) (Table 1, entry 1 vs 2). This small variation in the purity of the complex afforded undecanal (**2**) in moderate yield (54%) along with some of undecanyl undecanoate (**4**), which was produced presumably by the oxidation of acetal **3** (Scheme 1).

Although the reaction was slower at room temperature, some of the aldehyde was obtained (entry 3). Further prolonging the

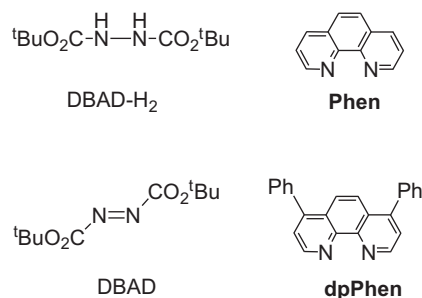


Figure 1. Structure of reagents used in oxidation reactions.

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**Table 1**  
Optimization of the reaction conditions

Entry	Alcohol	Conditions				Product	Yield (%)
		Phen/CuCl (mol %)	Co-catalyst (mol %)	Temp (°C)	Period (h)		
		$\text{alcohol} \xrightarrow[\text{O}_2, \text{ Tol, temp (}^\circ\text{C), period (h)}]{\text{CuCl / Phen (mol \%)} \\ \text{co-catalyst \{DBAD-H}_2 \text{ or DBAD (mol \%)\}} \\ \text{K}_2\text{CO}_3 \text{ (200 mol \%)}} \text{aldehyde or ketone}$					
1	Undecan-1-ol ( <b>1</b> )	5 <sup>a</sup>	DBAD-H <sub>2</sub> (5)	90	17	Undecanal ( <b>2</b> )	13 <sup>b</sup>
2	<b>1</b>	5 <sup>c</sup>	DBAD-H <sub>2</sub> (5)	90	0.5	<b>2</b>	54 <sup>b</sup>
3	<b>1</b>	5 <sup>c</sup>	DBAD-H <sub>2</sub> (5)	rt	22	<b>2</b>	31 <sup>b</sup>
4	<b>1</b>	5 <sup>d</sup>	DBAD-H <sub>2</sub> (5)	rt	40	<b>2</b>	41 <sup>b</sup>
5 <sup>e</sup>	<b>1</b>	5 <sup>d</sup>	DBAD-H <sub>2</sub> (5)	rt	40	<b>2</b>	46 <sup>b</sup>
6 <sup>e</sup>	Undecan-2-ol ( <b>5</b> )	5 <sup>d</sup>	DBAD (5)	rt	24	Undecan-2-one ( <b>6</b> )	69 <sup>f</sup>
7 <sup>e</sup>	<b>5</b>	5 <sup>d</sup>	DBAD (5)	rt	48	<b>6</b>	86 <sup>f</sup>
8 <sup>e</sup>	<b>5</b>	10 <sup>d</sup>	DBAD (10)	rt	48	<b>6</b>	97 <sup>f</sup>

<sup>a</sup> CuCl (95% purity, guaranteed reagent, Nacalai<sup>5</sup>).

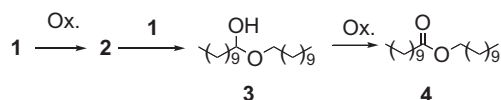
<sup>b</sup> GC-yields.

<sup>c</sup> CuCl was prepared by the reaction of CuCl<sub>2</sub> (98% purity, guaranteed reagent, Nacalai) with Na<sub>2</sub>SO<sub>3</sub> (98% purity, guaranteed reagent, Nacalai).

<sup>d</sup> CuCl was prepared by the reaction of CuCl<sub>2</sub> (99.999% purity, Aldrich) with Na<sub>2</sub>SO<sub>3</sub> (99.99% purity, Aldrich).

<sup>e</sup> K<sub>2</sub>CO<sub>3</sub> was dried over P<sub>2</sub>O<sub>5</sub> under reduced pressure at 70 °C for 24 h.

<sup>f</sup> Isolated yields.



**Scheme 1.** Reaction mechanism for the formation of ester **4**.

reaction time did not affect the yield because of the generation of ester **4**. With the enhancement of the activity of catalyst in mind, we tested the reactivity of highly pure CuCl (CuCl<sub>2</sub> (99.999% purity) with Na<sub>2</sub>SO<sub>3</sub> (99.99% purity)), and confirmed that this reagent was more reactive (entry 4). Moreover, the yield was increased by using K<sub>2</sub>CO<sub>3</sub> dried over P<sub>2</sub>O<sub>5</sub> under reduced pressure at 70 °C for 24 h (entry 5). However, since ester **4** was still generated, we shifted our focus to the oxidation of the secondary alcohol, undecan-2-ol (**5**). Using highly pure CuCl with dried K<sub>2</sub>CO<sub>3</sub>, undecan-2-one (**6**) was obtained in 69% after 24 h at room temperature (entry 6), and a prolonged reaction time (48 h) gave a better yield, up to 86% of the ketone (entry 7). When 10 mol % of catalyst was employed, the ketone was obtained in excellent yield (entry 8).

For further improvements, we examined the effects of using 1,10-phenanthroline derivatives<sup>6</sup> and bases instead of non-substituted 1,10-phenanthroline and K<sub>2</sub>CO<sub>3</sub>, respectively, and ultimately found that 4,7-diphenyl-1,10-phenanthroline (**dpPhen**, see Fig. 1) combined with Cs<sub>2</sub>CO<sub>3</sub> (98% purity)<sup>7</sup> made a remarkable difference (Table 2). The results shown in Table 2 can be summarized as follows:<sup>8</sup> (1) Highly pure (99.995+%) CuCl (Aldrich) catalyzed the oxidation effectively. (2) The reaction of most of the alcohols proceeded smoothly within a few hours even under atmospheric pressure using air at room temperature. (3) All of the alcohols tested were converted sufficiently into the corresponding ketones in efficient yields, even in the reactions with non-allylic or -benzylic secondary alcohols.<sup>9</sup> (4) Reaction conditions were so mild that no or little racemization was observed in the oxidation of a mixture of *cis*- and *trans*-2-benzylcyclohexanol (**7**)<sup>10</sup> having the *R*-configuration at the C-2 position to form (2*R*)-2-benzylcyclohexanone (**8**) with 92% ee after 3 h and 90% ee after 24 h, respectively.<sup>12</sup>

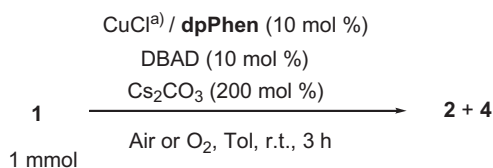
Thus, these modifications of Markó's procedure dramatically increased the reactivity of the oxidation reactions. We then returned

**Table 2**  
Oxidation of secondary alcohols

Alcohol	CuCl <sup>(a)</sup> / <b>dpPhen</b> (10 mol %)		Product	Yield (%)
	DBAD (10 mol %)	Cs <sub>2</sub> CO <sub>3</sub> (200 mol %)		
	$\text{R}^1\text{CH(OH)R}^2 \xrightarrow[\text{Air, Tol (1 ml), r.t., Period}]{\text{DBAD (10 mol \%)} \\ \text{Cs}_2\text{CO}_3 \text{ (200 mol \%)}} \text{R}^1\text{C(O)R}^2$			
	3			99
	3			93
	3			99
	3			94
	3 36			39 84
	2			93
	1			100
	3			100
	3			99
	3 24			78 90

<sup>a</sup> CuCl (99.995+% purity, Aldrich).

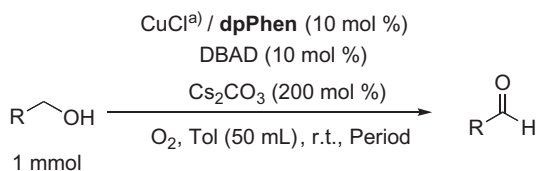
**Table 3**  
Optimization of the reaction conditions for **1**

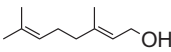
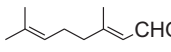
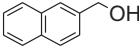
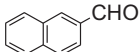
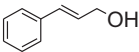
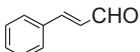


Entry	Conditions			Yield of <b>2 + 4</b> (%)	Ratio ( <b>2/4</b> )
	Tol (mL)	Concn (M)	Oxidizing agent		
1	1	1.0	Air	57	3/1
2	10	0.1	Air	89	7/1
3	20	0.05	Air	84	>10/1
4	50	0.02	Air	54	>20/1
5	50	0.02	O <sub>2</sub>	98	>20/1

<sup>a</sup> CuCl (99.995+% purity, Aldrich).

**Table 4**  
Aerobic oxidation of primary alcohols



Alcohol	Period (h)	Product	Yield (%)
	1		97
	3		94
	3		100

<sup>a</sup> CuCl (99.995+% purity, Aldrich).

our focus to the reaction of primary alcohols. Using the same conditions for the oxidation of secondary alcohols, we were able to convert undecanol to a mixture of aldehyde **2** and ester **4** in 57% yield in a 3:1 ratio that favored the aldehyde (Table 3, entry 1). However, the production of **4** could be limited by conducting the reaction under dilute conditions (entries 2 and 3). Furthermore, although higher dilution of the reagents slowed the reaction, we obtained very little ester **4** (entry 4). Finally, the use of molecular oxygen gave satisfactory results (entry 5). Under the same highly diluted conditions, a few primary alcohols were oxidized successfully to afford the corresponding aldehydes (Table 4).

In conclusion, we have modified Markó's aerobic oxidation procedure and have successfully oxidized primary and secondary alcohols to the corresponding aldehydes and ketones in excellent yield under mild conditions using highly pure (99.995+%) CuCl with 4,7-diphenyl-1,10-phenanthroline (**dpPhen**), DBAD, and Cs<sub>2</sub>CO<sub>3</sub> (98% purity).

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- We tested several commercially available 1,10-phenanthrolines such as 5-chloro-, 5-nitro-, 5,6-dimethyl-, and 4,7-diphenyl-1,10-phenanthroline.
- Highly pure Cs<sub>2</sub>CO<sub>3</sub> (99.995%, Aldrich) could not improve the efficiency of oxidation any more.
- Typical procedure for oxidation: To a suspension of CuCl (9.9 mg, 0.10 mmol, 99.995+% purity, Aldrich) in toluene (1 mL) was added 4,7-diphenyl-1,10-phenanthroline (**4**) (33.5 mg, 0.1 mmol) to form a dark blue solution. After 10 min, DBAD (23.4 mg, 0.1 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (650 mg, 2 mmol) were added to the solution and stirred for 5 min. Alcohol (1 mmol) was added and the resulting mixture was left to stir for 3 h at room temperature under atmospheric pressure of air without a cover (when O<sub>2</sub> was used, an oxygen balloon covered the flask). The reaction progress was monitored by TLC. After completion, the mixture was filtered through Celite and evaporated. The residue was purified by SiO<sub>2</sub> column chromatography (hexane/ACoEt = 10:1/3:1) to afford the ketone or aldehyde.
- All of resulting ketones were known compounds and their spectra were compared with authentic samples.
- The mixture of alcohols (*cis/trans* = 1/2.4) was prepared by the reduction of (2*R*)-2-benzylcyclohexanone<sup>11</sup> (92% ee) with LAH.
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- The optical purity was determined by HPLC analysis using a chiral column (Daicel: chiralcell OJ).