

Efficient, recoverable, copper-catalyzed aerobic oxidation of alcohols under FBS and thermomorphic mode

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Abstract—A series of fluorinated bipyridine derivatives, (4,4'-bis(R_fCH₂OCH₂)-2,2'-bpy) {R_f = *n*-C₈F₁₇ (**1a**), *n*-C₉F₁₉ (**1b**), *n*-C₁₀F₂₁ (**1c**), *n*-C₁₁F₂₃ (**1d**)} have been successfully synthesized using 4,4'-bis(bromomethylene)-2,2'-bpy and fluorinated alkoxides. Bpy **1a–d** have been characterized by multi-nuclei (¹H, ¹⁹F, and ¹³C) NMR, GC/MS and FTIR. The Cu complexes **2a–d** could be generated in situ by stirring ligands **1a–d** with CuBr·Me₂S at room temperature, respectively. The 3-component systems **3c–d**, CuBr·Me₂S/Bpy (**1c–d**)/2,2,6,6-Tetramethylpiperidine 1-oxyl (TEMPO), were successfully used to the aerobic oxidation of alcohols under the fluororous biphasic system (FBS). The resulting products from FBS could be easily recovered by two phase separation with high yields up to 8 runs (>90%). In order to avoid using the expensive fluororous solvents, systems **3a–d**, CuBr·Me₂S/Bpy (**1a–d**)/TEMPO, were also successfully shown to catalyze the aerobic alcohol oxidation under the thermomorphic condition (in C₆H₅Cl), and the yields of oxidation of 4-nitrobenzyl alcohol were close to 100% even after 8 runs. In particular, **3a** was most effective under the thermomorphic mode in the chemoselectivity of aerobic oxidation of aliphatic primary alcohols to aldehydes without any overoxidized acids. © 2007 Elsevier Ltd. All rights reserved.

1. Introduction

The oxidation of alcohols to aldehydes or ketones is one of the important transformations in organic synthesis.^{1–4} Although several metal-based oxidizing reagents have been developed, these reagents usually require stoichiometric amounts of metal oxidants, and thus a large amount of waste is formed. In this respect, the oxidation of alcohols using molecular oxygen catalyzed by recoverable catalysts is ideal from an environmental and atom-economical viewpoint.⁵ Knochel and co-workers⁶ reported the utility of fluororous biphasic catalysis^{7,8} for oxidation reactions.⁹ In such a system, perfluoroalkylated catalysts have been used to achieve a selective solubility in fluororous solvents, whereas the reagents and starting materials are soluble in the organic phase. This method allows a facile separation of the catalyst from the product by decantation of the fluororous phase. Although FBS combines the advantages of homogeneous catalysis and heterogeneous catalysis, the large-scale use of perfluorocarbon solvents has some drawbacks: high cost and

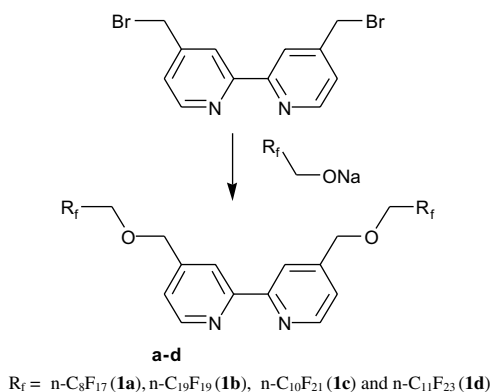
environmental persistence. In response to these limitations, several research groups, for example, Gladysz and co-workers^{10,11} and Yamamoto and co-workers,^{12,13} have introduced some new methodologies. For example, the solubility based thermomorphic properties of catalysts in an organic solvent were evaluated as a new strategy to perform homogeneous catalysis without the use of fluororous solvents.

Reported here are the synthesis of novel ligands **1a–d**, and using systems **3a–d**, CuBr·Me₂S/Bpy/2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), as catalysts in the aerobic oxidation of alcohols under (a) fluororous biphasic system and (b) thermomorphic mode.

As shown in Scheme 1, the preparation of fluororous-ponytailed 2,2'-bpy ligands started from deprotonation of readily available fluororous alkanols, R_fCH₂OH, where R_f = *n*-C₈F₁₇ (**a**), *n*-C₉F₁₉ (**b**), *n*-C₁₀F₂₁ (**c**), and *n*-C₁₁F₂₃ (**d**). Fluororous alkanols, R_fCH₂OH, were treated with CH₃ONa solution (30% in CH₃OH) to give the corresponding alkoxides. The alkoxides were then reacted with 4,4'-bis(BrCH₂)-2,2'-bpy^{14–16} to give rise to [4,4'-bis(R_fCH₂OCH₂)-2,2'-bpy] (**1a–d**) with high yields. The novel ligands of this type were successfully synthesized in our group for the first time.¹⁷ The partition ratios of ligands **1a–d** are shown in Table 1. Based on

Keywords: Fluorinated bipyridine; Fluororous biphasic system; Aerobic oxidation; Alcohols; Thermomorphic.

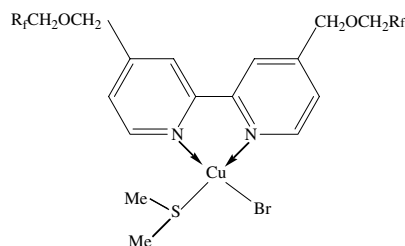
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Scheme 1. Syntheses of ligands **1a-d**.Table 1. Distribution ratios of ligands **1a-d** in different solvent systems

Ligand	CH ₂ Cl ₂ /FC77	DMF/FC77	C ₆ H ₅ Cl/FC77
1a (F%:59.8)	1.07:1	1:4.5	2.6:1
1b (F%:61.2)	1.04:1	1:6.9	1.09:1
1c (F%:62.3)	1:42	~0.1:100	1:29
1d (F%:63.3)	1:70	<0.1:100	1:48

the partition value in C₆H₅Cl/FC77 system, we selected the two high fluorine-content ligands **1c,d** under FBS for the aerobic alcohol oxidation. Interestingly, ligands **1a-d** were also found to be useful for the aerobic alcohol oxidation under the thermomorphic mode. Because Cu complexes **2a-d** were found soluble in DMF at 90 °C, but **2a-d** precipitated at 25 °C or below. Because of the wide availability of fluorinated alcohols, a range of these novel bpy-based ligands **1a-d** could then be studied and gave the insightful information based on the different lengths of fluorinated ponytails. As shown in Figure 1, the possible structure of Cu complexes **2a-d** is believed to be 4-coordinate geometry¹⁸ as proposed by Tavener and Clark. Subsequently, we focused on the catalytic ability of the Cu systems **3a-d**, which is based on the 3-component system, CuBr·Me₂S/Bpy/TEMPO, in this Letter.

The Cu complexes **2a-d** could be generated in situ by stirring ligands **1a-d** with CuBr·Me₂S at room temperature, respectively. The resulting systems **3a-d**, CuBr·Me₂S/Bpy (**1a-d**)/TEMPO, could be used for aerobic alcohol oxidation as shown in Figure 2. Knochel and co-workers⁶ reported the fluorinated alkylated bpy ligand (ligand A) in their studies on the alcohol oxida-

Figure 1. The proposed structure of Cu complex **2a-d**.¹⁸

tion using four –CH₂– units as a spacer and only one type of fluorinated ligand, which was made from C₈F₁₇(CH₂)₃I. In contrast, in this study both **1c** and **1d** could be used as bpy-based ligands for the aerobic oxidation of alcohols under FBS as shown in Table 2. System **3c**, based on ligand **1c**, could catalyze the aerobic oxidation of 4-nitrobenzyl alcohol with good yields and excellent recycling abilities up to eight times. System **3d**, based on ligand **1d**, could also catalyze the same reaction with the good yields up to five times. During the separation and recycling,¹⁹ Cu complexes **2c-d** were easier to be recovered by FBS, but the effect of the electron-withdrawing from longer fluorinated ponytail in **2d** on the Cu center seemed to slow down catalytic activities.

In order to demonstrate the generic application of Cu systems **3c,d** to the aerobic alcohol oxidation under FBS, the aerobic oxidation of benzylic, allylic, and aliphatic alcohols (1° or 2°) was also tested using **3c-d**. The results showed excellent yields during 3–8 h catalysis for benzylic and allylic alcohols (entries 1–4) listed in Table 3, but no reactions were observed with aliphatic alcohols (entries 5 and 6). The possible reason was that the unactivated aliphatic alcohols were much more difficult to be oxidized. When we compared these results with the results obtained by Knochel co-workers,⁶ ligands **1c,d** were shown to be almost as good as ligand A in the aerobic oxidation of activated alcohols. Ligands **1c,d** which have a shorter spacer (–CH₂OCH₂–) may have made Cu center less reactive than ligand A with a 5-bond spacer, –(CH₂)₄–. However, ligands **1c-d** could be easily prepared with high yields from cheaper and widely available fluorinated alcohols and therefore, could be good replacements.

A series of fluorinated bpy-based ligands (including **1a-d**) were prepared in our group, and their unusual thermomorphic properties were found to be similar to what were reported by Gladysz et al. and Yamamoto et al.^{10–13} It was interesting to observe ligands **1c-d** and their resulting complexes exhibiting the exponential increases in solubility when the temperature was raised. This property has made the homogeneously recoverable catalyst to precipitate at room temperature possible.

The systems **3a-d** were used to homogeneously catalyze the aerobic oxidation of alcohols (aromatic or aliphatic) under the thermomorphic mode (in C₆H₅Cl), and the catalysts could be recovered and reused eight times without any significant loss of activity. As shown in Table 4, systems **3a-d** could be effectively recycled for the aerobic oxidation of 4-nitrobenzyl alcohol. Due to the electronic effect of the longest fluorinated ponytail, **3d**-catalyzed aerobic oxidation of alcohols took longer time to complete, and the reaction yield decreased significantly after 6 runs. From the Table 4 results, one trend was observed: the shorter the fluorinated ponytail, the better the catalyst. Therefore, the catalytic abilities in the series were: **3a** > **3b** > **3c** > **3d**. Furthermore, the ICP-MS results from four cycles of **3d**-catalyzed oxidations showed an average 1.9% loss of Cu for each recovery. When the results from FBS and thermomorphic systems were compared (Tables 2 and 4), one could easily conclude

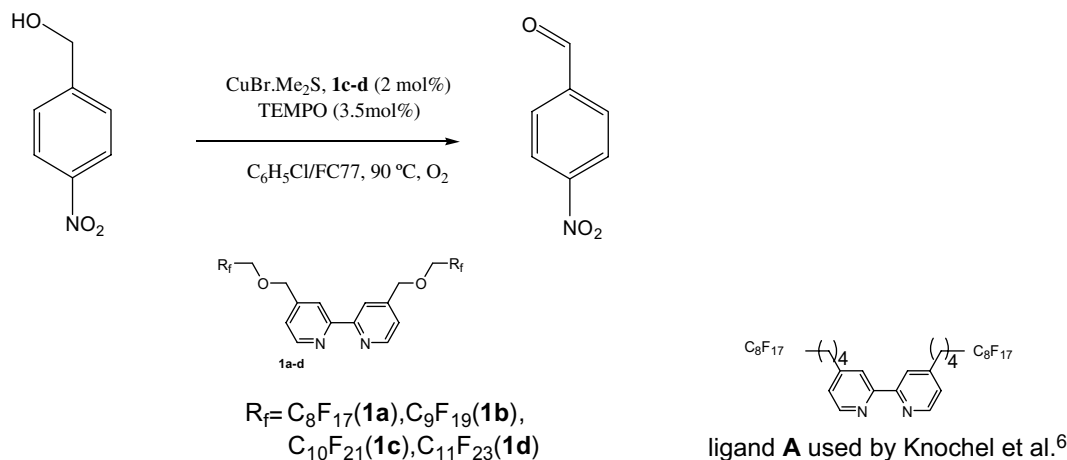


Figure 2. Aerobic oxidation of 4-nitrobenzyl alcohol to 4-nitrobenzaldehyde based on ligands **1c,d**; ligand **A**⁶ is shown for comparison.

Table 2. Oxidation of 4-nitrobenzyl alcohol under fluoruous biphasic system

Cycle no.	Yield ^a (%)		
	A ⁶	1c	1d
1	93	98	93
2	86	82	82
3	87	88	>99
4	88	100	>99
5	88	100	>99
6	85	100	63
7	81	100	NR ^b
8	86	>90	NR

TEMPO (3.5 mol %), CuBr·Me₂S, **1c,d** (2 mol %), 90 °C, O₂, 4–8 h.

^aThe yield was measured by GC/MS (NMP as internal standard).

^bNR: no reaction.

that the thermomorphic system was better in catalysis than FBS.

In addition, the pictures of the several stages of reactions are shown in **Figure 3**. (A) Before reaction, **2a** was insoluble; (B) the reactants were easily soluble in C₆H₅Cl, and **2a** was still insoluble; (C) during the catalysis, it was a homogenous catalysis when the temperature was around 80 °C; (D) At the end of reaction, the catalyst precipitated and was recovered for the next run when the product mixture was cooled to room temperature.

In order to test the general application of **3a–d** to the aerobic alcohol oxidations,^{20,21} a variety of alcohols were also tested under the thermomorphic mode as

Table 3. Aerobic oxidation of other alcohols under FBS

Entry	Substrate	Product	3c system		3d system	
			Time (h)	Yield (%)	Time (h)	Yield (%)
1			6	100	7	>99
2			5	100	3	>99
3			7	100	8	>99
4			6	100	5	>99
5	CH ₃ (CH ₂) ₈ CH ₂ OH	CH ₃ (CH ₂) ₈ CHO	NR ^a	NR	NR	NR
6			NR	NR	NR	NR

TEMPO (3.5 mol %), CuBr·Me₂S, **1c,d** (2 mol %), 90 °C, O₂.

^aNR: no reaction.

Table 4. Aerobic oxidation of 4-nitrobenzyl alcohol to 4-nitrobenzaldehyde by using systems **3a–d** under thermomorphic mode

Cycle no.	3a		3b		3c		3d	
	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)
1	5	93	5	99	5	>99	5	>99
2	4	97	4	97	2	96	5	96
3	4	>99	4	99	2	99	5	100
4	4	>99	4	95	3	100	5	100
5	4	>99	4	100	4	93	5	90
6	5	92.3	4	>99	4	88	6	89
7	4	95	7	>99	6	99	NR ^a	NR
8	6	>99	7	>99	13	80	NR	NR

TEMPO (3.5 mol %), CuBr·Me₂S, **1a–d** (2 mol %), 80–90 °C, O₂.

^aNR: no reaction.

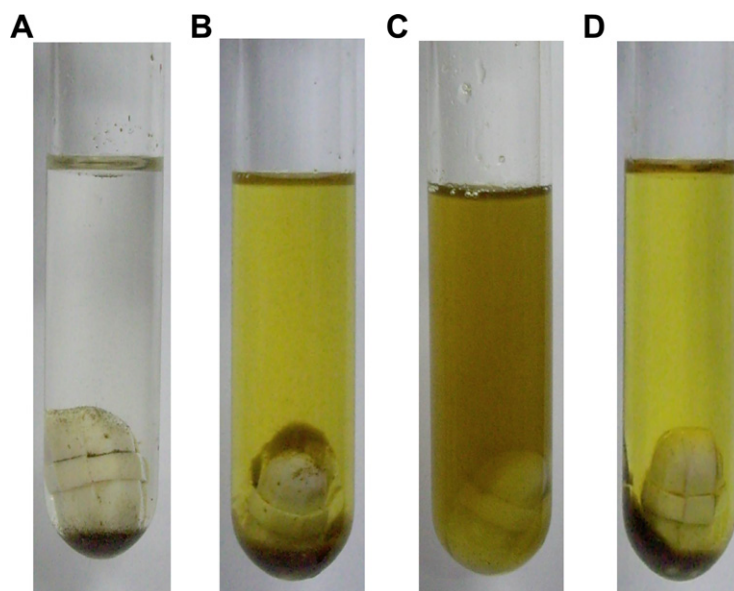


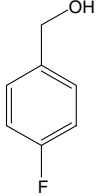
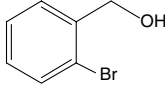
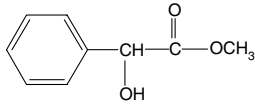
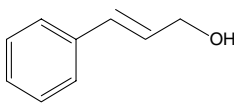
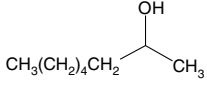
Figure 3. The pictures of the several stages of aerobic oxidation of 4-nitrobenzyl alcohol; (A) before reaction; (B) the reactants were easily soluble in C₆H₅Cl, and **2a** was insoluble; (C) during the catalysis, it was a homogenous catalysis at 80 °C; (D) at the end of reaction, the catalyst precipitated and was recovered for the next run.

shown in Table 5. The benzylic and allylic alcohols (entries a–d) could be easily oxidized by catalysts **3a–d** within 7 h. The reason why entry c took 16 h for the **3d**-catalyzed oxidation is mainly because of the steric hindrance of the substrate. The aliphatic 1° and 2° alcohols, the unactivated alcohols, could also be oxidized, but the amount of TEMPO used had to be raised to 10%. Both unactivated aliphatic alcohols, e and f, could then be oxidized in the thermomorphic mode, but not in the FBS (as shown in Table 3). The possible reason was because the single phase was more easily achieved in thermomorphic condition than in the fluorinated biphasic condition. The primary alcohol, 1-decanol, (entry e) could be oxidized with excellent yields. However, the secondary aliphatic alcohol due to the steric reason was only partially oxidized, and therefore, even after 17 h the best yield was only 43%. Overall, systems **3a–d**, CuBr·Me₂S/Bpy (**1a–d**)/TEMPO, were able to oxidize all classes of alcohols in the neutral condition under the thermomorphic mode, which suggests that the catalysts could then be easily recovered¹⁹ and reused.

To our surprise, all **3a–d** showed good chemoselectivity and excellent yields (>99%) to aldehydes in the aerobic oxidation of aliphatic 1° alcohols (Table 5; entry e) without the problem of over-oxidizing.²² In order to test this type of selective oxidation, other aliphatic 1° alcohols were also tested and were successfully oxidized by **3a**, with good yields, to aldehydes without trace of over-oxidized acids. As shown in Table 6, 1-octanol (entry i) was easily and selectively oxidized. The olefinic group (entry ii) as one functional group present in the molecule was undisturbed during the oxidation. When the bulky cyclohexyl group (entry iii) was present, oxidation also went smoothly. In particular, the heteroatom-containing (S or N atom) alcohol (entry iv or v) could also be oxidized without being influenced from its chelating effect. Therefore, **3a** can not only oxidize all classes of alcohols in neutral conditions, but also selectively oxidize primary alcohols (especially aliphatic) with no trace of over-oxidized carboxylic acids.

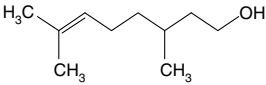
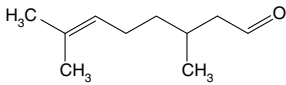
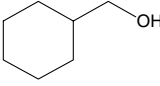
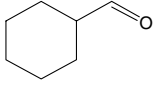
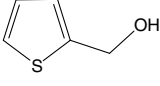
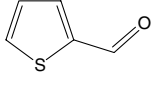
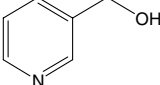
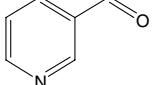
In summary, the novel ligands **1a–d** were successfully prepared with high yields, and the CuBr·Me₂S/Bpy

Table 5. Aerobic alcohol oxidations by systems **3a–d** under thermomorphic mode

Entry	Substrate	3a		3b		3c		3d	
		Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)
a		6	100	6	100	6	100	6	100
b		6	100	7	>99	6	100	5	100
c		7	100	7	100	6	100	16	100
d		6	100	6	93	6	100	5	100
e ^a	CH ₃ (CH ₂) ₈ CH ₂ OH	7	>99	7	100	7	>99	7	>99
f ^a		17	43	17	23	17	43	17	31

^a For entries e and f, the amount of TEMPO used was raised from 3.5% to 10%. In the **3a** case, when 3.5% TEMPO was used, the yield of entry e was 92.6% after 16 h.

Table 6. Aerobic oxidation of primary alcohols by systems **3a** under thermomorphic mode

Entry	Substrate	Product	3a	
			Time (h)	Yield (%)
i	CH ₃ (CH ₂) ₆ CH ₂ OH	CH ₃ (CH ₂) ₆ CHO	8	>99
ii			9	96
iii			8	>99
iv			8	>99
v			8	>99

TEMPO (10%); CuBr·Me₂S, **1c,d** (2 mol %), 80 °C, O₂; TOF: ca. 6.3 h⁻¹.

(**1a–d**)/TEMPO system was useful in the aerobic alcohol oxidation under the FBS and thermomorphic mode. The catalytic results from thermomorphic mode were better than from FBS. In the thermomorphic mode, **3a–d** could catalyze the oxidation of unactivated aliphatic alcohols as well as benzylic, allylic alcohols. The catalytic abilities within this series are **3a** > **3b** > **3c** > **3d**.

To our knowledge, besides the catalysts used by Yamaguchi and Mizuno³ and Markó et al.,²² systems **3a–d** were the 3rd system capable of oxidizing all classes of alcohols. In particular, it was shown that **3a** was recoverable and the most efficient in the series in the chemoselective oxidation of primary alcohols without adding bases under the thermomorphic mode.

2. Experimental

Thermomorph mode: For preparation of 4-nitrobenzaldehyde a 25 mL (Schlenk) flask was charged with the bipyridine **1a** (43 mg, 40 μ mol; 2 mol %) dissolved in FC77 (2 mL) and CuBr \cdot Me₂S (8.2 mg, 40 μ mol; 2 mol %) dissolved in a small amount of CH₃CN leading to a deep green solution. After evaporation, solid **2a** was formed. Then, a solution of 4-nitrobenzyl alcohol (306 mg, 2.0 mmol) and TEMPO (10.9 mg, 70 μ mol, 3.5 mol %) in chlorobenzene (2 mL) was added. Complex **2a** was not soluble in chlorobenzene at rt. However, when the mixture was stirred at 80 °C, it became one phase and then further stirred at 80–90 °C for several hours while a gentle O₂ stream was passing. At the end of the reaction, the mixture was cooled to 0 °C and the catalyst precipitated, the organic layer was decanted and the precipitated **2a** was recovered (and reused) after the centrifugation.

Acknowledgments

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Supplementary data

Syntheses of ligands **1a–d** and the catalytic reactions under FBS were described. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.074.

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