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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($R_fCH_2OCH_2$)-2,2′-bpy) {$R_f = n\text{-}C_8F_{17}$ (**1a**), $n\text{-}C_9F_{19}$ (**1b**), $n\text{-}C_{10}F_{21}$ (**1c**), $n\text{-}C_{11}F_{23}$ (**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 (^{1}H, ^{19}F, and ^{13}C) NMR, GC/MS and FTIR. The Cu complexes **2a**–**d** could be generated in situ by stirring ligands **1a**–**d** with $CuBr\cdot Me_2S$ at room temperature, respectively. The 3-component systems **3c**–**d**, $CuBr\cdot Me_2S$/Bpy (**1c**–**d**)/2,2,6,6-Tetramethylpiperidine 1-oxyl (TEMPO), were successfully used to the aerobic oxidation of alcohols under the fluorous 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 fluorous solvents, systems **3a**–**d**, $CuBr\cdot Me_2S$/Bpy (**1a**–**d**)/TEMPO, were also successfully shown to catalyze the aerobic alcohol oxidation under the thermomorphic condition (in C_6H_5Cl), 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.

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-workers[6] reported the utility of fluorous biphasic catalysis[7,8] for oxidation reactions.[9] In such a system, perfluoroalkylated catalysts have been used to achieve a selective solubility in fluorous 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 fluorous 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 fluorous solvents.

Reported here are the synthesis of novel ligands **1a**–**d**, and using systems **3a**–**d**, $CuBr\cdot Me_2S$/Bpy/2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), as catalysts in the aerobic oxidation of alcohols under (a) fluorous biphasic system and (b) thermomorphic mode.

As shown in Scheme 1, the preparation of fluorous-ponytailed 2,2′-bpy ligands started from deprotonation of readily available fluorous alkanols, R_fCH_2OH, where $R_f = n\text{-}C_8F_{17}$ (**a**), $n\text{-}C_9F_{19}$ (**b**), $n\text{-}C_{10}F_{21}$ (**c**), and $n\text{-}C_{11}F_{23}$ (**d**). Fluorous alkanols, R_fCH_2OH, were treated with CH_3ONa solution (30% in CH_3OH) to give the corresponding alkoxides. The alkoxides were then reacted with 4,4′-bis($BrCH_2$)-2,2′-bpy[14–16] to give rise to [4,4′-bis($R_fCH_2OCH_2$)-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

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

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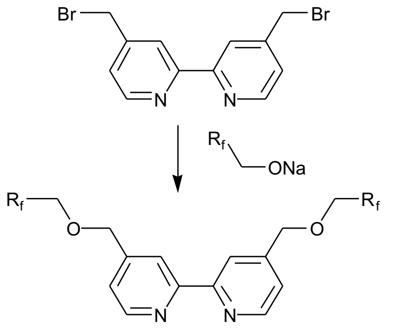

a-d

R_f = n-C_8F_{17} (**1a**), n-$C_{19}F_{19}$ (**1b**), n-$C_{10}F_{21}$ (**1c**) and n-$C_{11}F_{23}$ (**1d**)

Scheme 1. Syntheses of ligands **1a**–**d**.

Table 1. Distribution ratios of ligands **1a**–**d** in different solvent systems

Ligand	CH_2Cl_2/FC77	DMF/FC77	C_6H_5Cl/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 C_6H_5Cl/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 fluorous 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 fluorous ponytails. As shown in Figure 1, the possible structure of Cu complexes **2a**–**d** is believed to be 4-coordinate geometry[18] 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·Me_2S/Bpy/TEMPO, in this Letter.

The Cu complexes **2a**–**d** could be generated in situ by stirring ligands **1a**–**d** with CuBr·Me_2S at room temperature, respectively. The resulting systems **3a**–**d**, CuBr·Me_2S/Bpy (**1a**–**d**)/TEMPO, could be used for aerobic alcohol oxidation as shown in Figure 2. Knochel and co-workers[6] reported the fluorous alkylated bpy ligand (ligand **A**) in their studies on the alcohol oxidation using four $–CH_2–$ units as a spacer and only one type of fluorous ligand, which was made from $C_8F_{17}(CH_2)_3I$. 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 fluorous ponytail in **2d** on the Cu center seemed to slow down catalytic activities.

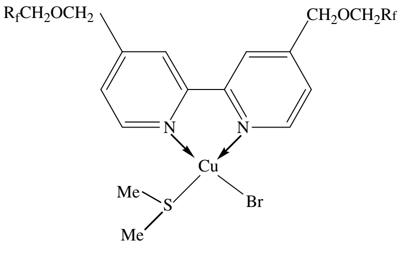

Figure 1. The proposed structure of Cu complex **2a**–**d**.[18]

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 ($–CH_2OCH_2–$) may have made Cu center less reactive than ligand **A** with a 5-bond spacer, $–(CH_2)_4–$. 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 C_6H_5Cl), 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 fluorous 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 fluorous 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