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Copper-Catalyzed α-Aminoxylation of Ketones with 2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO)

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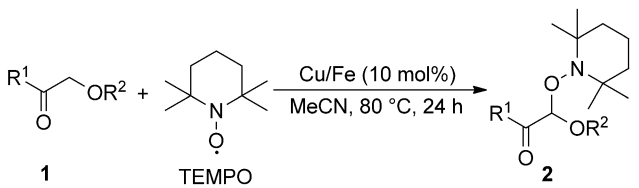
Abstract: An efficient copper-catalyzed α-aminoxylation of ketones with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) is presented for the synthesis of 2-aryloxy-1-aryl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)ethanones in moderate to excellent yields. It is noteworthy that the copper/iron (Cu/Fe) catalyst can be recovered and reused several times with high catalytic reactivity.

Keywords: α-aminoxylation; C–H cleavage; copper; ketones; TEMPO; 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)

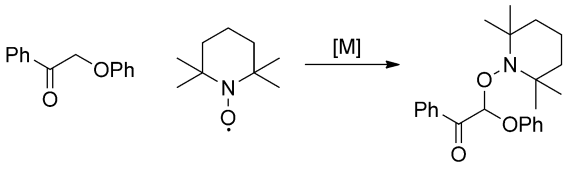
Oxygen-bearing stereocenters are fundamental structural units that are found in natural products and pharmaceutical agents.[1] Moreover, alkoxyamines can also be used not only as initiators for controlled radical polymerizations[2] but also as polymer light stabilizers, peroxide substitutes (rheology modifiers), or fireproofing agents.[3] There has been an ongoing interest in the development of simple, efficient methods for synthesizing *N*-alkoxyamines. To the best of our knowledge, however, the scope of substrates is limited to aldehydes, and other carbonyl compounds including ketones remain an unexploited area. For example, the MacMillan group[4] and the Zhong group[5] have independently reported L-proline-catalyzed enantioselective α-oxidation of aldehydes. Later, Sibi and coworkers[6] have described an alternative method for preparing alkoxyamines using an $FeCl_3$/amine organocatalyst system. Recently, the MacMillan group[7] and other groups[8] also developed some new approaches to the enantioselective α-oxidation of aldehydes using a synergistic combination of copper and organocatalysts. Despite impressive progress in transition metal-catalyzed oxyamination reactions, it is desirable that a transition metal catalyst be recoverable and reusable from environmental and atom-economical points of view. Herein we report a new and efficient route to the α-aminoxylation of 2-aryloxy-1-arylethanones with TEMPO[9] using a reusable Cu/Fe catalyst (Scheme 1).[10] This method is the first example for the Cu-catalyzed oxyamination reaction of ketones with TEMPO.

The reaction between 2-phenoxy-1-phenylethanone (**1a**) and TEMPO was investigated to optimize the reaction conditions, and the results are summarized in Table 1. The results demonstrated that the reaction could not take place without a metal catalysts (entry 1). However, only a trace of the target product, 2-phenoxy-1-phenyl-2-(2,2,6,6-tetramethyl-piperidin-1-yloxy)ethanone (**2a**), was observed in the presence of CuO (entry 2). To our delight, a 38% yield of product **2a** was obtained when the reaction was carried out using 10 mol% $Cu(OAc)_2$ catalyst (entry 3). Subsequently, other Cu catalysts, such as $CuCl_2$, $Cu(OTf)_2$, $CuSO_4$, CuI, Cu_2O, $CuBr_2$ and copper powders, were tested, we found that copper powders (purity: wt% Cu = 98.3938%) were more efficient, affording product **2a** up to 90% yield (entries 4–10), the yield was enhanced to 91% using the purity of 99.5 wt% Cu and to 92% yield at the purity of 99.999 wt% Cu (entries 11 and 12). On the contrary, the catalytic activities of Fe powers were decreased with increasing purity (entries 13–16). While commercially available common Fe powders (purity: wt%



Scheme 1. Copper-catalyzed α-oxyamination reaction.

Table 1. Screening for the optimal reaction conditions.[a]



Entry	[M] (mol%)	Solvent	T [°C]	Yield [%][b]
1	–	MeCN	80	0
2	CuO (10)	MeCN	80	trace
3	$Cu(OAc)_2$ (10)	MeCN	80	38
4	$CuCl_2$ (10)	MeCN	80	56
5	$Cu(OTf)_2$ (10)	MeCN	80	71
6	$CuSO_4$ (10)	MeCN	80	81
7	CuI (10)	MeCN	80	49
8	Cu_2O (10)	MeCN	80	41
9	$CuBr_2$ (10)	MeCN	80	54
10	Cu (98.3938%) (10)	MeCN	80	90
11	Cu (99.5) (10)	MeCN	80	91
12	Cu (99.999%) (10)	MeCN	80	92
13	Fe (88.2667%) (10)	MeCN	80	11
14	Fe (99.8%) (10)	MeCN	80	7
15	Fe (99.998%) (10)	MeCN	80	3
16	Fe on SiO_2 powder	MeCN	80	trace
17[c]	Cu/Fe (10)	MeCN	80	93
18[d]	Cu/Fe (10)	MeCN	45	73
19[e]	Cu/Fe (10)	MeCN	25	71
20	Cu/Fe (5)	MeCN	80	90
21	Cu/Fe (1)	MeCN	80	85
22	Cu/Fe (10)	DCE	80	15
23	Cu/Fe (10)	DMF	80	3
24	Cu/Fe (10)	toluene	80	<5
25[f]	Cu/Fe (10)	MeCN	80	89

[a] *Reaction conditions:* **1a** (0.2 mmol), TEMPO (1.1 equiv.), [M] and solvent (2 mL) for 24 h, Cu/Fe (wt%): 37.5000% Cu, 31.3000% Fe and about 31.2% SiO_2.
[b] Isolated yield.
[c] An old Cu/Fe catalyst (prepared over one year previously) was also tested, and it gave the identical results.
[d] Reaction time: 5 days.
[e] Reaction time: 7 days.
[f] **1a** (10 mmol) and Cu (0.075 mol%, Cu/Fe) for 24 h, and the TON was 118,000.

Fe = 88.2667%) afforded product **2a** in 11% yield (entry 13), the yield of **2a** was decreased to 7% using 99.5% purity Fe and to 3% yield with 99.998% purity Fe (entries 14 and 15). However, the use of Fe on SiO_2 powders resulted in no detectable product **2a** (entry 16). Interestingly, the reaction proceeded smoothly when 10 mol% Cu (Cu/Fe) was added, providing the expected product **2a** in 93% yield (entry 17). Among the reaction temperatures examined, it turned out that the reaction rate decreased when the temperature was lowered (entries 18 and 19). The amount of Cu/Fe was also evaluated, and the yield of **2a** was lowered slightly at 5 mol% or 1 mol% Cu/Fe (entry 17 *vs.* entries 20 and 21). Finally,

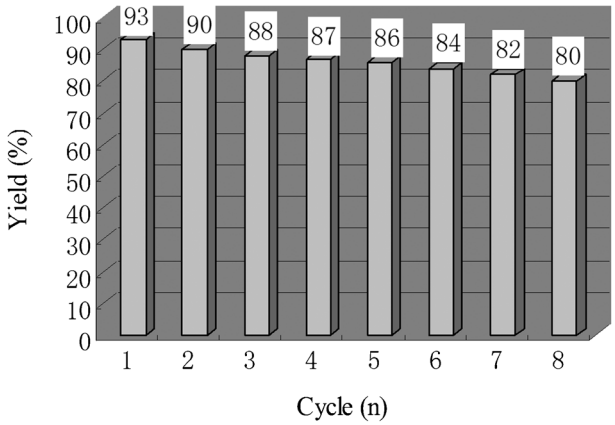


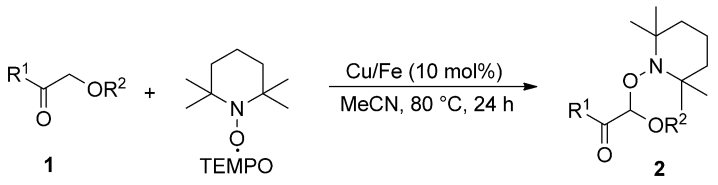
Figure 1. Recycling of the Cu/Fe catalyst.

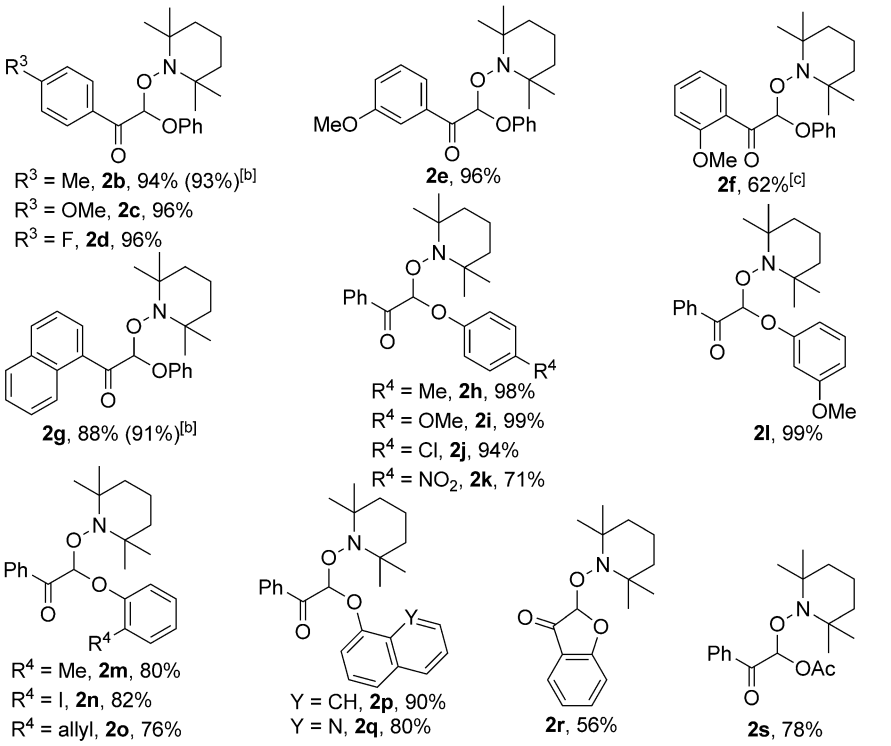
a number of solvents, DCE, DMF and toluene, was tested in the presence of the Cu on Fe catalyst: they were ineffective for the reaction (entries 22–24). It is noteworthy that the reaction can be carried out at relatively lower loading of Cu [0.075 mol% Cu (Cu/Fe)] to furnish the desired product **2a** in 89% yield for 24 h (TON = 118,000, entry 25).

Importantly, the copper on iron catalyst could be simply recovered and reused by use of magnetic forces (Figure 1). The catalytic reactivity of Cu/Fe was still high after eight runs of recycling and reuse, albeit with gradually decreasing the chemical yields. To elucidate these, a catalyst leaching experiment was performed (Scheme S1 in the Supporting Information). The experimental results revealed that catalyst leaching was observed. Thus, the reason for the gradually decreasing chemical yields is that some Cu/Fe catalyst was lost during both the reaction process and the post-treatment process.

As shown in Table 2, the scope of 2-aryloxy-1-arylethanones **1** with respect to TEMPO was explored under the optimal conditions. We were pleased to find that a variety of 2-aryloxy-1-arylethanones **1b–q** were compatible with the optimal conditions (products **2b–q**), and no obvious electronic effects of the aryl rings were observed. Initially, a number of substituents, including Me, MeO and F groups, on the aromatic ring of the arylethanone moiety were evaluated (products **2b–f**): they are viable for the reaction with TEMPO, and the reactive order of the substituents is *para* and *meta* > *ortho*. For examples, substrates **1b–1d** bearing Me, F or MeO groups gave the corresponding products **2b–d** in good yields. Gratifyingly, treatment of 1-(naphthalen-1-yl)-2-phenoxyethanone (**1g**) with TEMPO afforded the desired product **2g** in 88% yield. Extensive screening revealed that substituents such as Me, MeO, Cl, I, NO_2 and allyl groups, on the aromatic ring of the phenoxy moiety were well tolerated (Products **2h–o**). For instance, *p*-Me- or *p*-MeO-substituted substrates **1h** and **1i** underwent the

Table 2. Cu-catalyzed oxyamination of ketones **1** with TEMPO.[a]



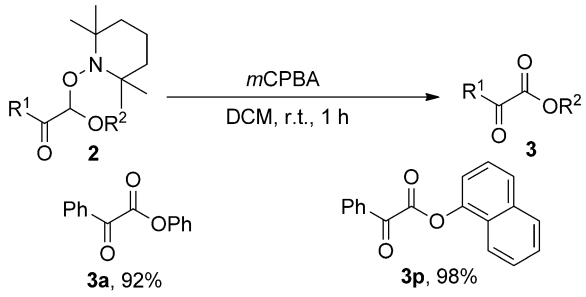


[a] *Reaction conditions:* **1** (0.2 mmol), TEMPO (1.1 equiv.), Cu/Fe (10 mol%) and MeCN (2 mL) at 80 °C for 24 h.
[b] 1 mmol scale of substrate **1** was tested, and the yield is given in the parenthesis after 24 h.
[c] For 36 h.

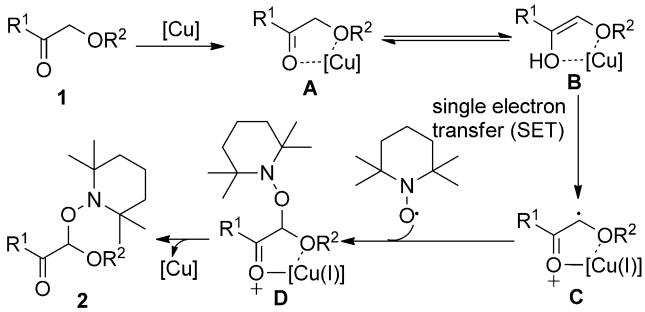
reaction with TEMPO smoothly, providing the corresponding products **2h** and **2i** in quantitative yields. Interestingly, the optimized conditions were compatible with both 2-(naphthalen-1-yloxy)-1-phenylethanone (**1p**) and 1-phenyl-2-(quinolin-8-yloxy)ethanone (**1q**) (products **2p** and **2q**). It was noted that benzofuran-3(2*H*)-one (**1r**) was found to be a suitable substrate with TEMPO, leading to the desired product **2r** in 56% yield. Using AcO-substituted substrate **1s**, a good yield was still achieved under the optimal conditions (product **2s**).

Aryl glyoxylate motifs play an important role in biological processes as useful intermediates in the synthesis of some natural products, such as the 3-deoxy-2-ulosonic acids and their derivatives.[11] Compounds **2a** and **2p** could react under the reported methods[11] to give the corresponding products **3a** and **3p** in 92% and 98% yields, respectively (Scheme 2).

A possible mechanism as outlined in Scheme 3 was proposed.[6–8] Complexation of substrate **1** with the active [Cu] species affords intermediates **A** and **B**. Intermediate **C** is generated from intermediate **B** by a single electron transfer (SET) process. The addition



Scheme 2. Utilizations of products **2a** and **2p**.



Scheme 3. Possible mechanism.

of TEMPO to intermediate **C** readily takes place leading to intermediate **D**. Finally, reductive elimination of intermediate **D** releases the desired product **2** and regenerates the active [Cu] species.

In summary, we have established the first example of the oxyamination of 2-aryloxy-1-arylethanones with TMEPO for the synthesis of substituted alkoxyamines using the Cu/Fe catalyst. Importantly, the Cu/Fe catalyst could retain its catalytic reactivity after several recyclings. Work to extend the reaction and application of this Cu/Fe catalyst is currently underway in our laboratory.

Experimental Section

Typical Experimental Procedure for the Copper-Catalyzed α-Aminoxylation Reaction

To a Schlenk tube were added α-arlyoxyacetophenones **1** (0.2 mmol), 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) **2** (1.2 equiv.), 10 mol% Cu (Cu/Fe = 3.4 mg) and MeCN (2 mL). Then the contents of the tube was stirred at 80 °C for the indicated time until complete consumption of starting material as monitored by TLC and/or GC-MS analysis. After the reaction was finished, the reaction mixture was washed with brine. The aqueous phase was re-extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, concentrated under vacuum, and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate) to afford the pure product.

2-Phenoxy-1-phenyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)ethanone (2a): White soild, mp 77.8–78.6 °C (uncorrected); ^{1}H NMR (500 MHz): δ = 8.27 (d, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.02 (s, 1H), 1.59–1.45 (m, 5H), 1.37 (s, 3H), 1.32–1.31 (m, 1H), 1.21 (s, 3H), 1.16 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (125 MHz): δ = 192.6, 156.7, 133.4, 133.0, 130.4, 129.4, 128.2, 122.0, 109.8, 61.1, 60.0, 40.1, 40.0, 33.8, 33.1, 20.9, 20.2, 17.0; IR (KBr): ν = 1687, 1507 cm^{-1}; LR-MS (EI, 70 eV): *m/z* (%) = 367 (M^+, 1), 352 (1), 183 (3), 156 (100); HR-MS (EI): *m/z* = 368.2230, calcd. for $C_{23}H_{30}NO_3$ [$(M+H)^+$]: 368.2226.

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