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Copper-Catalyzed Aminoxylation of Different Types of Hydrocarbons with TEMPO: A Concise Route to *N*-Alkoxyamine Derivatives

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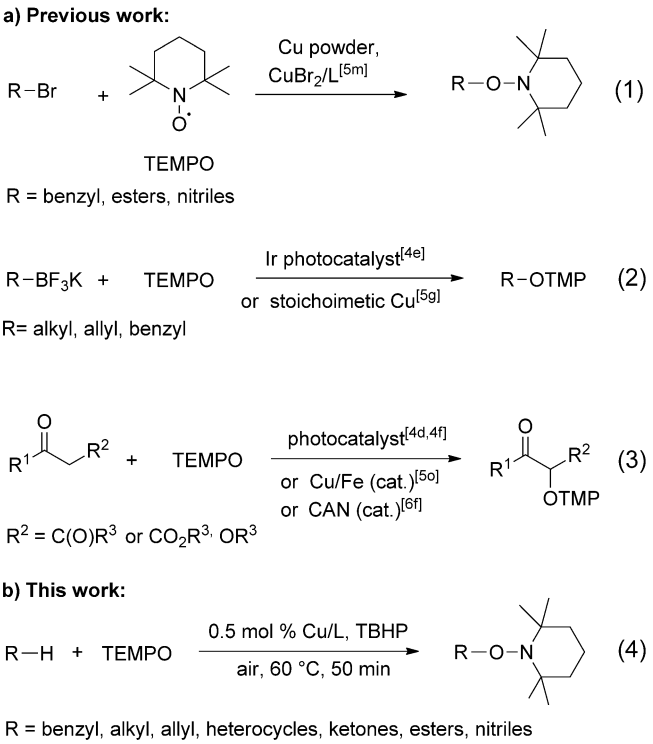
Abstract: An efficient copper(II)/*tert*-butyl hydroperoxide catalyst system [(Bpy)Cu(II)/TBHP] for the aminoxylation of different types of hydrocarbons under mild and ambient air conditions has been developed to furnish *N*-alkoxyamine derivatives in good to high yields. Ketones, esters, nitriles, toluene, ethylbenzene, heterocycles, cyclohexene, and cyclohexanes are well compatible in this system and the catalyst loading could be lowered to 0.5 mol%.

Keywords: *N*-alkoxyamines; *tert*-butyl hydroperoxide (TBHP); copper catalysis; hydrocarbons; 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO)



Scheme 1. Methods towards the preparation of *N*-alkoxyamine derivatives.

N-Alkoxyamines are widely recognized as effective initiators in controlled radical polymerization.[1] They provide powerful methods for controlling the polydispersity and molecular weight of growing polymer chains. In addition, *N*-alkoxyamines are also applied as chiral building blocks, fireproofing agents, rheology modifiers,[2] as well as polyfunctional precursors especially in biologically active natural products and pharmaceutical agents.[3]

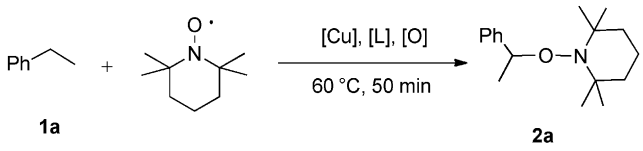
Therefore, the development of approaches for preparing *N*-alkoxyamines has witnessed substantial progress in the past decades.[4–6] Several classical approaches were notable for the synthesis of *N*-alkoxyamines.[4–6] The most classical method was reported by Matyjaszewski and co-workers,[5m] in which *N*-alkoxyamines were formed by treatment of an alkyl bromide with TEMPO (2,2,6,6-tetramethylpiperidine *N*-oxyl) catalyzed by CuBr. Notably, this alkyl radical intermediate was generated from the reaction of alkyl bromide and CuBr [Scheme 1, Eq. (1)]. Analogous approaches using alkyl trifluoroborates instead of alkyl bromides were discovered under Cu or photocatalyst systems [Scheme 1, Eq. (2)].[4e,5g] An improved approach was reported by Frey and co-workers,[5n] wherein the way to generate hydrocarbyl radicals was entirely different *via* hydrogen atom abstraction of hydrocarbon compounds catalyzed by copper halide and onium iodide in the presence of TBHP. However, a narrow substrate scope limited its practicability. Only three substrates were investigated. Moreover, Tan[4d] and Koike[4f] respectivly reported photocatalyst

catalyzed α-aminoxylation of 1,3-dicarbonyl compounds with TEMPO in the presence of photoredox catalysts such as organic dyes or iridium complexes. In 2013, Li and co-workers[5o] developed a reusable Cu/Fe catalyst for α-aminoxylation reactions between ketones with TEMPO. More recently, Jiao and co-workers[6f] first demonstrated a CAN-catalyzed α-aminoxylation of 1,3-dicarbonyl compounds with TEMPO [Scheme 1, Eq. (3)]. Other examples were found for the synthesis of the *N*-alkoxyamine derivatives.[4–6] However, in most of the aforementioned cases, there has been evidently limitation in substrate scope. Therefore, a more simple and compatible protocol remains in demand.

Here we disclose an efficient (Bpy)Cu(II)/TBHP catalyst system for the aminoxylation of different types of hydrocarbons under mild and ambient air conditions [Scheme 1, Eq. (4)]. This catalyst system shows excellent reactivity and general substrate scope, and the catalyst loading can be lowered to 0.5 mol%.

In the initial studies, we chose ethylbenzene (**1a**) as a model substrate to test the α-aminoxylation reaction with TEMPO. The optimization results are summarized in Table 1. To our surprise, when **1a** was treated with 2 equivalents of TBHP (aqueous 65%) without adding any metal catalysts under air at 60 °C, an 81% yield of the desired α-aminoxylated product **2a** was observed after 21 h (Table 1, entry 1). With this promising result in hand, further screening of catalysts revealed that the combination of $Cu(OAc)_2$/bpy (2,2′-bipyridine) (20 mol%) could dramatically accelerate the reaction to provide **2a** in 96% yield within 50 min. To our delight, it was found that a decrease of catalyst loading did not impact on the efficiency of this reaction (Table 1, entries 2–4). When using as little as 0.5 mol% of $Cu(OAc)_2$/bpy catalyst, a pleasing 97% yield of product **2a** was obtained within 50 min (Table 1, entry 4). To evaluate the reactivity of other copper salts for this transformation, various Cu(II) and Cu(I) species were then examined, showing that these copper salts could promote the aminoxylation reaction to form the desired product **2a** in 43–92% yields (Table 1, entries 5–11). These results indicated that cupric or cuprous complexes are able to serve as an efficient catalyst. By varying the ligands, we found that 2,2′-bipyridine is still the best ligand for this reaction (Table 1, entries 12–15). In addition, the yield of the reaction was not significantly affected in the absence of ligand, but the reaction time was prolonged to 3 h (Table 1, entry 16). Next, a series of oxidants was explored. Dramatically, no desired product was obtained when employing Oxone, *m*CPBA, H_2O_2, BPO, $K_2S_2O_8$, DTBP, and CH_3COOOH as oxidants (Table 1, entries 17–19, 21–24). By running the reaction at 100 °C with H_2O_2, a trace amount of desired product **2a** was observed (Table 1, entry 20). CHP

Table 1. Optimization of the reaction conditions.[a]



1a **2a**

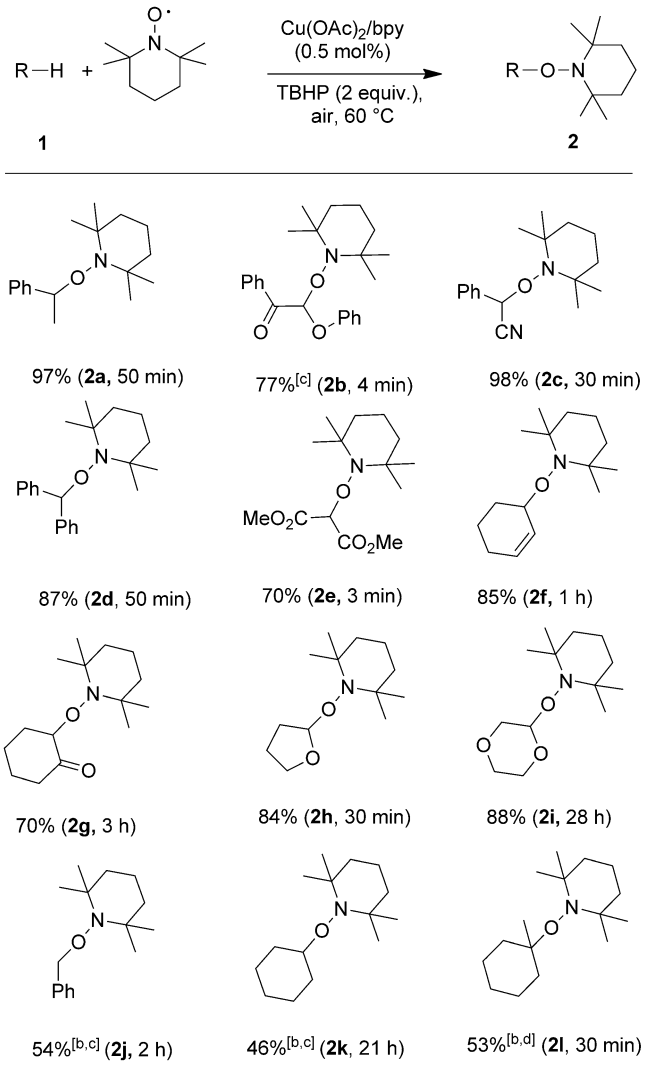
Entry	[Cu] (mol%)	[L] (mol%)	[O] (2 equiv.)	Yield [%][b]
1[c]	–	–	TBHP	81
2	$Cu(OAc)_2$ (20)	Bpy (20)	TBHP	96
3	$Cu(OAc)_2$ (5)	Bpy (5)	TBHP	95
4	$Cu(OAc)_2$ (0.5)	Bpy (0.5)	TBHP	97
5	CuOAc (0.5)	Bpy (0.5)	TBHP	86
6	CuBr (0.5)	Bpy (0.5)	TBHP	73
7	CuCl (0.5)	Bpy (0.5)	TBHP	92
8	CuI (0.5)	Bpy (0.5)	TBHP	79
9	$Cu(TFA)_2 \cdot x\,H_2O$ (0.5)	Bpy (0.5)	TBHP	75
10	$Cu(NO_3)_2 \cdot 3\,H_2O$ (0.5)	Bpy (0.5)	TBHP	43
11	$Cu(OTf)_2$ (0.5)	Bpy (0.5)	TBHP	88
12	$Cu(OAc)_2$ (0.5)	1,10-phen (0.5)	TBHP	93
13	$Cu(OAc)_2$ (0.5)	TMEDA (0.5)	TBHP	84
14	$Cu(OAc)_2$ (0.5)	pyridine (0.5)	TBHP	51
15	$Cu(OAc)_2$ (0.5)	Bpym (0.5)	TBHP	61
16[d]	$Cu(OAc)_2$ (0.5)	–	TBHP	90
17	$Cu(OAc)_2$ (0.5)	Bpy (0.5)	Oxone	n.r.
18	$Cu(OAc)_2$ (0.5)	Bpy (0.5)	*m*CPBA	n.r.
19	$Cu(OAc)_2$ (0.5)	Bpy (0.5)	H_2O_2	n.r.
20[e]	$Cu(OAc)_2$ (0.5)	Bpy (0.5)	H_2O_2	10
21	$Cu(OAc)_2$ (0.5)	Bpy (0.5)	BPO	n.r.
22	$Cu(OAc)_2$ (0.5)	Bpy (0.5)	$K_2S_2O_8$	n.r.
23	$Cu(OAc)_2$ (0.5)	Bpy (0.5)	DTBP	n.r.
24	$Cu(OAc)_2$ (0.5)	Bpy (0.5)	CH_3COOOH	n.r.
25	$Cu(OAc)_2$ (0.5)	Bpy (0.5)	CHP	75
26[f]	$Cu(OAc)_2$ (0.5)	Bpy (0.5)	TBHP	57
27[g]	$Cu(OAc)_2$ (0.5)	Bpy (0.5)	TBHP	trace
28[h]	$Cu(OAc)_2$ (0.5)	Bpy (0.5)	TBHP	93
29[i]	$Cu(OAc)_2$ (0.5)	Bpy (0.5)	TBHP	92
30[j]	$Cu(OAc)_2$ (20)	Bpy (20)	–	11
31[k]	$Cu(OAc)_2$ (0.5)	Bpy (0.5)	TBHP	23

[a] *Conditions:* TEMPO (0.3 mmol), **1a** (10 equiv.), $Cu(OAc)_2$ (0.5 mol%), bpy (0.5 mol%), oxidant (2 equiv.), air, 60 °C, 50 min.
[b] Isolated yield.
[c] 21 h.
[d] 3 h.
[e] 100 °C, 48 h.
[f] 100 °C.
[g] Room temperature.
[h] under O_2, 2 h.
[i] Under N_2.
[j] 150 °C, 4 h.
[k] **1a** (1 equiv.), 4 h. TBHP = *tert*-butyl hydroperoxide, *m*CPBA = *meta*-chloroperoxybenzoic acid, BPO = benzoyl peroxide, DTBP = di-*tert*-butyl peroxide, 1,10-phen = 1,10-phenanthroline, TMEDA = tetramethylethylenediamine, Bpym = 2,2′-bipyrimidine, CHP = cumyl hydroperoxide, n.r. = no reaction.

(cumyl hydroperoxide), which has a similar structure to TBHP, was used as an oxidant to give the desired product **2a** with 75% yield (Table 1, entry 25). These results demonstrated that TBHP is critical for the generation of free radicals in this transformation. Upon heating to 100 °C with TBHP, an obviously decreased yield was obtained (57%, Table 1, entry 26), implying that a higher temperature might lead to the decomposition of product **2a**. Two control experiments were run under N_2 or O_2 atmosphere, both giving an excellent yield of **2a**, indicating that oxygen did not play a role in this transformation (Table 1, entries 28 and 29). Consequently, the optimal conditions are 0.5 mol% $Cu(OAc)_2$/bpy and TBHP (2 equiv.) under an air atmosphere at 60 °C within 50 min (Table 1, entry 4).

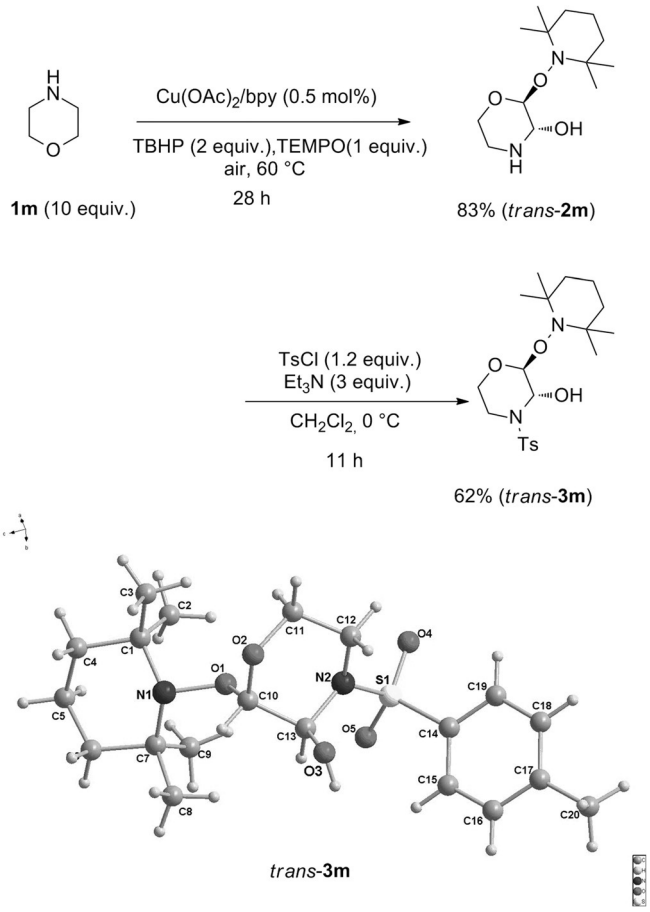
With the optimal reaction conditions in hand, next, we explored the scope and the utility of the reaction with various kinds of hydrocarbons. To our surprise, this catalyst system shows excellent reactivity and broad scope of substrates, including ketones, esters, nitriles, toluene, ethylbenzene, heterocycles, cyclohexene and cyclohexanes. Under the standard conditions, they generally furnished the desired *N*-alkoxyamine products in good to high yields (Table 2). For example, the treatment of ketone **1b** (2-phenoxy-1-phenylethanone) with TEMPO afforded the desired *N*-alkoxyamine product **2b** in 77% yield within 4 min. Gratifyingly, when using 2-phenylacetonitrile **1c** as a substrate, an excellent result (98% yield) was obtained in 30 min. Furthermore, diphenylmethane (**1d**) and dimethyl malonate (**1e**) reacted well under the standard conditions, giving the corresponding products in 87 and 70% yields, respectively. Notably, cyclohexene (**1f**) and cyclohexanone (**1g**) were found to be suitable substrates for this aminoxylation reaction, leading to the desired products **2f** and **2g** in 85% and 70% yields. It is worth noting that heterocycles, such as THF (**1h**) and 1,4-dioxane (**1i**), could be converted into their corresponding products in 84 and 88% isolated yields, respectively. Toluene **1j** was tolerated and gave the desired **2j** in 54% yield. Owing to the difficulty of hydrogen atom abstraction from cyclohexane (**1k**), the reaction of **1k** with TEMPO resulted in a decreased yield (46% for **2k**) despite using 4 equivalents of TBHP. In particular, when methylcyclohexane (**1l**) was subjected to the standard conditions, a tertiary carbon free radical was selectively formed and subsequently reacted with TEMPO to give the desired *N*-alkoxyamine **2l** in 53% yield. Several by-products from the coupling of secondary carbons in **1l** with TEMPO were found, but the tertiary carbon displayed highly reactivity. Consequently, the wide range of substrate scope demonstrated the practicability of this protocol for preparing various kinds of *N*-alkoxyamine derivatives.

Table 2. Scope of the copper-catalyzed aminoxylation reaction with TEMPO.[a]



[a] *Conditions:* TEMPO (0.3 mmol), **1a** (10 equiv.), $Cu(OAc)_2$ (0.5 mol%), bpy (0.5 mol%), TBHP (aqueous 65%, 2 equiv.), air, 60 °C, 4 min–42 h, isolated yield.
[b] TBHP (aqueous 65%, 4 equiv.).
[c] 100 °C.
[d] 80 °C.

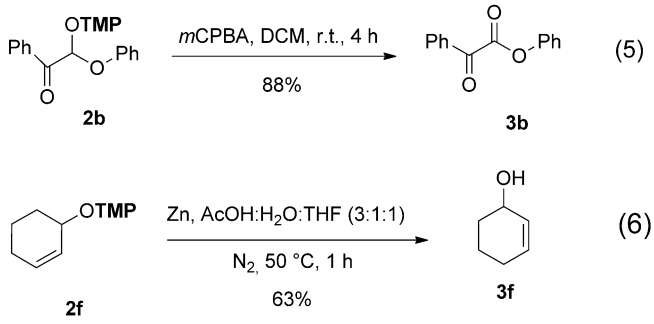
However, when using morpholine (**1m**) as a substrate, it afforded the unexpected product *trans*-**2m** in 83% yield. In order to determine the structure of *trans*-**2m**, the derivation of the unexpected product *trans*-**2m** was conducted by treatment of *trans*-**2m** with TsCl to provide compound *trans*-**3m** which was confirmed by single crystal X-ray analysis (Scheme 2).[7] For pyrrolidine, the reaction gave an unknown product, the structure of which was not defined well. Therefore, *N*-containing heterocyclic substrates gave abnormal products and the mechanism is unclear at present.



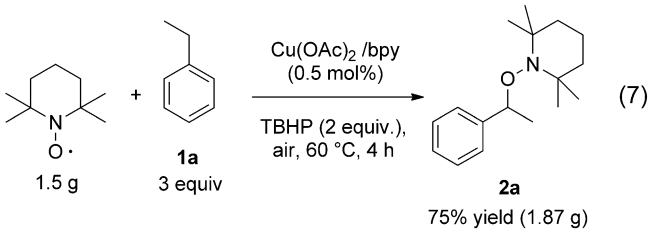
Scheme 2. The derivation of *trans*-**2m** and X-ray structure of *trans*-**3m**.

N-Alkoxyamines are versatile building blocks from the view of organic synthetic chemistry because they can be transformed into different compounds such as ketones by oxidation and alcohols by reduction, and can be used as a controller of weight in polymer chemistry. The representative transformation of *N*-alkoxyamines is illustrated in Scheme 2. For example, compound **2b** was treated with *m*CPBA in DCM to give phenyl 2-oxo-2-phenylacetate **3a** in 88% yield [Scheme 3, Eq. (5)], which is a common motif in biologically active natural products, for example, 3-deoxy-2-ulosonic acids and their derivatives.[8] In addition, the preparation of allyl alcohols is an important investigation area in organic chemistry. To our delight, compound **2f** was smoothly converted to cyclohex-2-enol **3f** in 63% yield by treatment with excess zinc powder in acetic acid at 50 °C for 1 h [Scheme 3, Eq. (6).[3c] Furthermore, the *N*-alkoxyamines could be easily transformed into carbocycles and lactones as reported by the Studer group.[9]

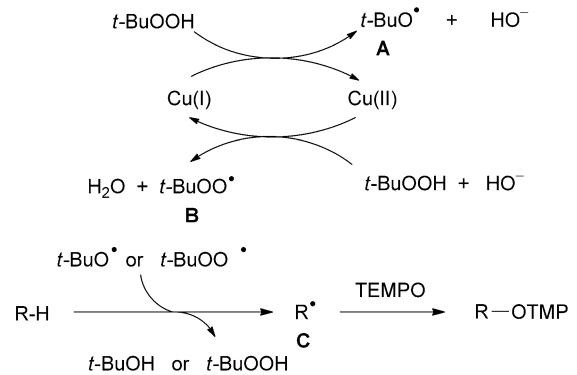
To display the usefulness and practicability of this method, we tested this reaction in a large scale. Ethylbenzene **1a** was chosen as a representative example. When 1.5 g of TEMPO were treated with 3 equivalents of ethylbenzene (**1a**) under the standard conditions, a 75% yield of compound **2a** (1.87 g) was obtained [Eq. (7)].



Scheme 3. Transformation and application of *N*-alkoxyamine derivative.



For the reaction mechanism, we proposed a possible reaction mechanism for copper-catalyzed aminoxylation of hydrocarbons with TEMPO. As outlined in Scheme 4, initially, the Cu catalyst is hypothesized to promote the decomposition of TBHP to generate *t*-BuO• radical **A** and *t*-BuOO• radical **B**.[10] Consequently, both cupric and cuprous catalysts could be responsible for this transformation (See Table 1, entries 4–11). When RH reacts with *t*-BuOO• or *t*-BuO• radical, the hydrocarbyl free radical **C** is smoothly provided by hydrogen atom abstraction. Subsequently, it is trapped by TEMPO to afford the corresponding *N*-alkoxyamine products.



Scheme 4. Proposed reaction pathway.

In conclusion, we have developed a general and practical protocol for the synthesis of *N*-alkoxyamines using the TEMPO, (Bpy)Cu(II) (0.5 mol%)/TBHP system. This system displays highly efficient reactivity for this transformation, giving the desired *N*-alkoxyamines in high to excellent yields under mild and air conditions within a short time. The investigation of the reaction′s generality reveals a broad substrate scope. The different types of substrates, such as ketones, esters, nitriles, toluene, ethylbenzene, heterocycles, cyclohexene, and cyclohexanes, are weel compatible in this system. Moreover, the reaction is easily handled because the color of TEMPO provides a useful visual indication for the progress of reaction and purification. Further studies on the reaction mechanism, the scope of the reaction and the potential application of this reaction are ongoing in our laboratory.

Experimental Section

General Remarks

All experiments were carried out under air. Reactions were monitored using thin-layer chromatography (TLC). ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DMX-400 at 400 and 100 MHz, respectively. High resolution mass spectra were obtained with ACQUITYTM UPLC & Q-TOF MS Premier Spectrometer. Mass spectra were determined on an HPLC-MS LCQ Advantage Thermo Finningan instrument. GC-MS analysis was performed on LECO Pegasus 4D GC× GC-TOFMS. Infrared (IR) spectra were recorded on an AVATAR 370 Spectrometer.

Synthesis of 2,2,6,6-Tetramethyl-1-(1-phenylethoxy)-piperidine (2a) as an Example

Under air, TEMPO (46.8 mg, 0.3 mmol), ethylbenzene **1a** (0.37 mL, 3 mmol), $Cu(OAc)_2$ (0.27 mg, 0.5 mol%), bpy (0.23 mg, 0.5 mol%), TBHP (aqueous 65%, 92.8 μL, 0.6 mmol) were added into a Schlenk tube. The reaction was stirred at 60 °C for 50 min. Upon completion, the mixture was purified by column chromatography (hexane/ethyl acetate) to give the colorless oil **2a**; yield: 97%.

Acknowledgements

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[7] CCDC 1425394 (*trans*-**3m**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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