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Copper-Catalyzed Aerobic C–H Trifluoromethylation of Phenanthrolines

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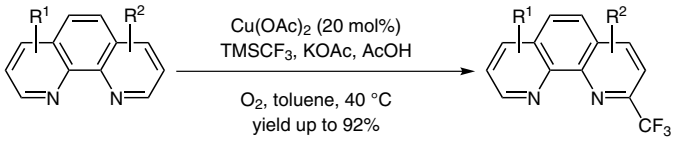

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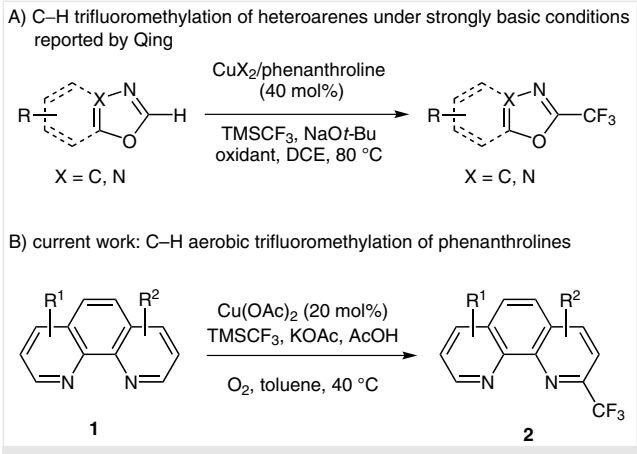
Abstract Direct C–H trifluoromethylation of heterocycles is a valuable transformation. In particular, nonprecious metal-catalyzed C–H trifluoromethylation processes, which do not proceed through CF_3 radical species, have been less developed. In this cluster report, a new copper-catalyzed aerobic C–H trifluoromethylation of phenanthrolines is described. This transformation affords trifluoromethylated phenanthrolines that have not been synthesized and preliminary mechanistic studies suggest that the CF_3 group transfer may occur through cooperative activation.

Key words copper, fluorine, oxygen, oxidation, heterocycles

Trifluoromethylated arenes and heterocycles are important building blocks for organic synthesis and pharmaceutical research because of their unique electronic and metabolic properties applicable to drug discovery.[2] Among various catalytic trifluoromethylation methods,[3] the direct C–H trifluoromethylation is a straightforward means to afford trifluoromethylated heterocycles. For example, methods for arene C–H trifluoromethylation initiated by CF_3 radical species has received much attention: MacMillan, Baran, and Sanford have each independently discovered radical-based methods for heterocycle trifluoromethylation.[4] In parallel, nonradical-based methods for C–H trifluoromethylation offer complementary synthetic utilities. Yu, Sanford, and Liu have reported the palladium-catalyzed C–H trifluoromethylation methods of heterocycles.[5] However, nonprecious metal-catalyzed direct C–H trifluoromethylation which does not proceed through CF_3 radical species has been less explored.

Recently, Qing disclosed a copper-catalyzed oxidative trifluoromethylation of heteroarenes under strongly basic conditions (Scheme 1,A).[6] In this reaction, a reductive elimination step of a CF_3 group from the high-valent copper center has been proposed as the key step for the C–H trifluoromethylation. Since phenanthrolines are widely used ligands in synthetic chemistry and to the best of our knowledge, the synthesis of trifluoromethylated phenanthrolines has not been reported,[7] we herein describe a $Cu(OAc)_2$-catalyzed method for aerobic C–H trifluoromethylation of phenanthrolines under nearly neutral conditions (Scheme 1,B). Our preliminary studies reveal that the acetate counterion is crucial for this unique reactivity and that the CF_3-group transfer may occur via Lewis acid–Lewis base cooperative activation.

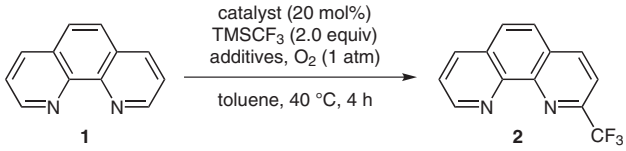


Scheme 1 Copper-catalyzed nonradical-based C–H trifluoromethylation of heteroarenes

We initiated catalyst discovery with 1,10-phenanthroline (**1**) as a model substrate for synthetic and mechanistic considerations (Table 1).[8] When KF was applied to activate $TMSCF_3$ under O_2 (1.013 bar), we observed that **1** was mostly recovered in the absence of copper catalyst (Table 1, entry 1). CuI and $CuBr_2$ were subsequently determined ineffective to promote the desired reaction (Table 1, entries 2 and 3). Interestingly, CuOAc catalyzes the *ortho* trifluoromethylation of **1** at 40 °C (Table 1, entry 4, full conversion, 72% yield), and $Cu(OAc)_2$ is equally active for this reaction (Table 1, entry 5, 75% yield). After exploring the counterion effect with a variety of copper(II) salts, we determined that $Cu(OAc)_2$ is superior to $Cu(TFA)_2$ and that $Cu(OTf)_2$ and $CuSO_4$ are unreactive (Table 1, entries 6–8). Surprisingly, we discovered that, in the absence of KF, $Cu(OAc)_2$ catalyzes this reaction, albeit with a lower yield (Table 1, entry 9, 58%

yield). Extensive optimization reveals that the combination of $Cu(OAc)_2$–KOAc or $Cu(OAc)_2$–KOAc–AcOH promotes the C–H oxidative trifluoromethylation with excellent yield (Table 1, entries 10 and 11). It is interesting to note that no bis-trifluoromethylation products were isolated even when a large excess amount of $TMSCF_3$ (>5.0 equiv) was applied and that the reaction under air atmosphere did not proceed as efficiently as the one that proceeded under O_2.

Table 1 Catalyst Discovery for Direct Phenanthroline Trifluoromethylation



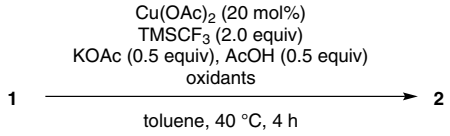
Entry[a]	Catalyst	Additive (equiv)	Conversion (%)[b]	Yield (%)[c]
1	none	KF (3.0)	<5	<5
2	CuI	KF (3.0)	<5	<5
3	$CuBr_2$	KF (3.0)	<5	<5
4	CuOAc	KF (3.0)	>95	72
5	$Cu(OAc)_2$	KF (3.0)	>95	75
6	$Cu(TFA)_2$	KF (3.0)	78	56
7	$Cu(OTf)_2$	KF (3.0)	<5	<5
8	$Cu(SO_4)_2$	KF (3.0)	<5	<5
9	$Cu(OAc)_2$	none	100	58
10	$Cu(OAc)_2$	KOAc (1.0)	100	78
11	$Cu(OAc)_2$	KOAc (0.5) AcOH (0.5)	100	80

[a] Reactions were carried out under O_2 at 40 °C, unless stated otherwise.
[b] Conversions were determined by ^1H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard.
[c] Isolated yield.

Since the facile conversion of copper(I) to copper(II) under aerobic conditions is well-known, we suspected that $Cu(OAc)_2$ is the active oxidative species. To test this hypothesis, we conducted the reaction with a stoichiometric amount of $Cu(OAc)_2$ in the absence of O_2 and observed full recovery of the starting material (Table 2, entry 1). This result suggests that copper(II) unlikely acts alone as the oxidant. We further explored a range of oxidants, including iodine(III), iodine(V), silver(I), DDQ, and TBHP, all of which proved ineffective for this reaction (Table 2).

Under optimized conditions, we evaluated a series of symmetric and desymmetric phenanthrolines for the *ortho* trifluoromethylation (Table 3). Symmetric 4,7-diphenyl phenanthroline proves an excellent substrate (Table 3, entry 2, 92% yield); however, 4,7-dimethylphenanthroline has a lower reactivity with a decreased yield (Table 3, entry 3, 61% yield). Desymmetric 3-phenylphenanthroline is an acceptable substrate for the *ortho* trifluoromethylation at the C-2 position (Table 3, entry 4, 64% yield) and symmetric 3,8-diphenylphenanthroline provides the trifluoromethylation product in a moderate yield (Table 3, entry 5, 52%). The trifluoromethylation of 5-nitrophenanthroline provides two readily separable products with a decent combined yield (Table 3, entry 6).

Table 2 Oxidant Sreening for the $Cu(OAc)_2$-Catalyzed Phenanthroline Trifluoromethylation

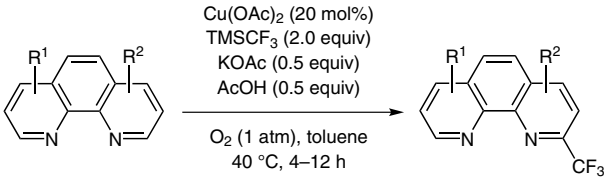


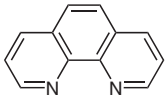
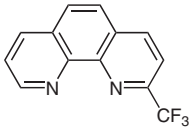
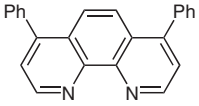
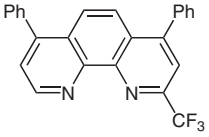
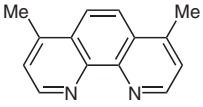
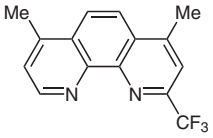
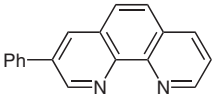
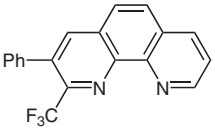
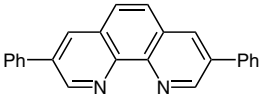
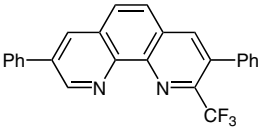
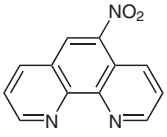
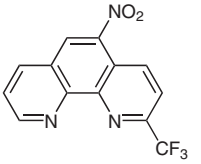
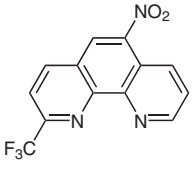
Entry	Oxidant	Conversion (%)	Yield (%)
1	none	<5	<5
2	O_2	>95	80
3	$PhI(OAc)_2$	56	42
4	AgOAc	<5	<5
5	DDQ[a]	15	10
6	DMP[b]	35	22
7	TBHP[c]	<5	<5

[a] DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.
[b] DMP: Dess–Martin periodinane.
[c] TBHP: *tert*-butyl hydroperoxide.

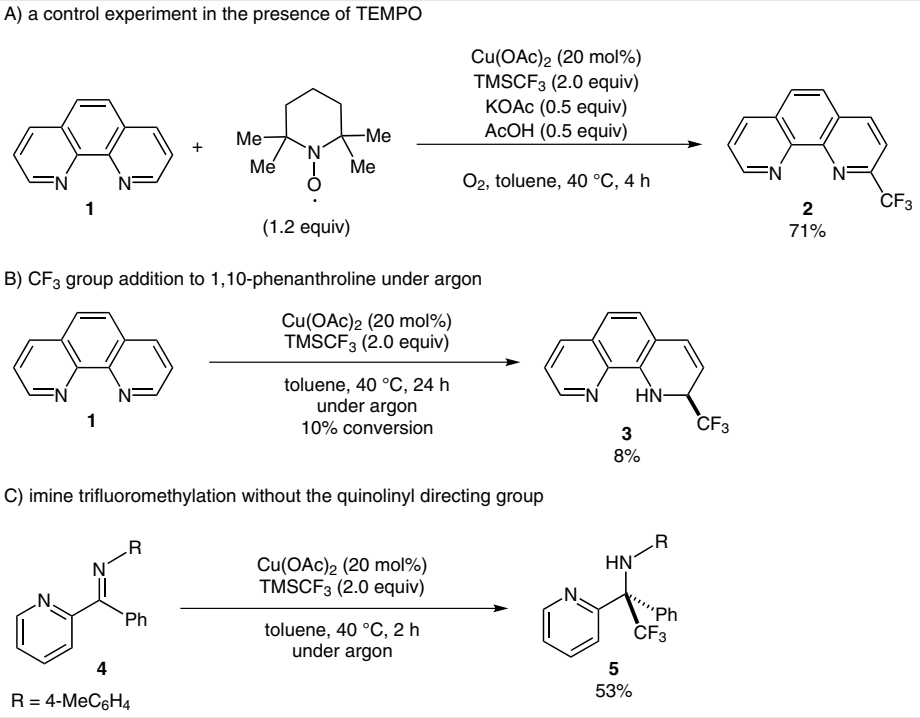
Intrigued by the dominant *ortho* selectivity and the fact that the catalytic cycle turns over in the absence of any fluoride-based activator, we then carried out several control experiments to probe for a possible mechanism (Scheme 2). First, when a stoichiometric amount of TEMPO was applied to the standard conditions, the product was isolated with a good yield (71% yield). At the same time, we did not detect any TEMPO–CF_3 adduct (Scheme 2,A). This result suggests that the CF_3 radical is unlikely to be involved in this reaction. Next, when we subjected **1** to catalytic conditions under an argon atmosphere, a trifluoromethyl-group addition product 1,2-dihydrophenanthroline **3** was isolated after 24 hours albeit with a low yield (Scheme 2,B). Subsequently, we tested the reactivity of an aniline-derived ketoimine **4** with an *ortho*-pyridyl moiety under an argon atmosphere and observed the imine trifluoromethylation product **5** with an acceptable yield (Scheme 2,C). These results suggest that an N,N-bidentate directing group is crucial for the copper-catalyzed CF_3-group transfer.

Table 3 Substrate Scope for the Copper-Catalyzed Trifluoromethylation of Phenanthrolines

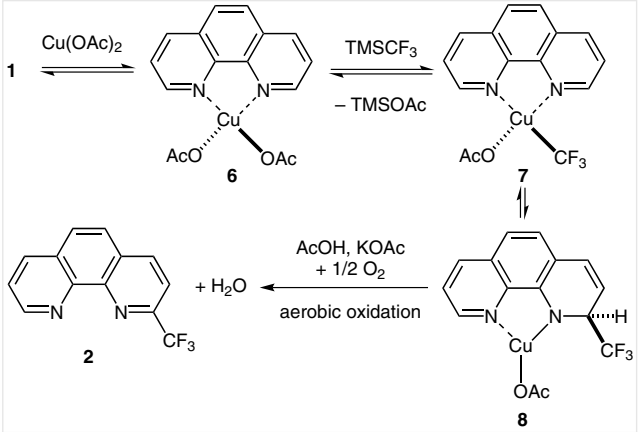


Entry	Substrate	Product	Yield (%)
1			80
2			92
3			61
4			64
5			52
6			17
			54

Based on the collective results from the control experiments, we propose the following mechanistic working hypothesis (Scheme 3). Since copper(II) is known to coordinate with **1** and generate the tetrahedral complex **6**,[9] the acetate ligand may be activated by the substrate **1**. Subsequently, the acetate ligand may then activate the CF_3 group from $TMSCF_3$ through a hypervalent silicon species. From this anionic metathesis, a Cu(CF_3)(OAc)(phenanthroline) intermediate **7** can be generated. Since the C=N bond of a phenanthroline is prone to nucleophilic addition,[10] the co-



Scheme 2 Control experiments for mechanistic insights



Scheme 3 Mechanistic working hypothesis for the copper-catalyzed aerobic C–H trifluoromethylation of phenanthroline

ordination of the substrate to the Lewis acidic copper(II) presumably activates the C=N bond to nucleophilic addition.[11] At the same time, the coordination of the Lewis basic substrate may cooperatively enhance the nucleophilicity of the CF_3 group. The addition product **8**, a 1,2-dihydrophenanthroline derivative can then undergo aerobic oxidation in the presence of O_2 to furnish **2**.[12,13]

In summary, we have discovered a new copper-catalyzed aerobic C–H trifluoromethylation of phenanthrolines. Our preliminary mechanistic studies revealed that a Lewis acid–Lewis base cooperative activation mechanism may be involved and that the reaction does not proceed through a CF_3 radical species. Further exploration with this new trifluoromethylation mechanism is ongoing.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379319.

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(1) These two authors contributed equally.
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(10) For an example of nucleophilic addition to the C=N bond of 1,10-phenanthroline, see: Nishikawa, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2011**, *133*, 8432.

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(13) **Typical Experimental Procedure**

To a mixture of 1,10-phenanthroline (**1**, 36 mg, 0.2 mmol), $Cu(OAc)_2$ (7.4 mg, 0.04 mmol), KOAc (9.8 mg, 0.1 mmol), and AcOH (6.0 μL, 0.1 mmol) in toluene (4.0 mL), $TMSCF_3$ (30 μL, 0.2 mmol) was added at room temperature under an O_2 atmosphere. The reaction mixture was stirred at 40 °C for 3 h. Another portion of $TMSCF_3$ (30 μL, 0.2 mmol) was added, and stirring was continued at 40 °C. The reaction was monitored by TLC. After the starting material was completely consumed, the reaction was quenched by H_2O and extracted with EtOAc (3 × 4 mL). The combined organic layer was washed by brine, dried over Na_2SO_4, and concentrated in vacuo. The product **2** was isolated through a silica gel flash column (40% EtOAc in hexanes) as a white foam (41 mg, 80% yield).

2-(Trifluoromethyl)-1,10-phenanthroline (2)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.24 (s, H_a), 8.38 (d, *J* = 8.4 Hz, H_f), 8.23 (d, *J* = 8.6 Hz, H_c), 7.93 (d, *J* = 8.4 Hz, H_g), 7.85, 7.78 (d, *J* = 8.8 Hz, H_d and H_e), 7.65 (m, H_b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.06, 147.7 (q, *J* = 35.0 Hz), 145.72, 145.56, 137.83, 136.09, 129.76, 129.10, 128.79, 125.70, 123.59, 124.30 (q, *J* = 273 Hz), 119.00 ppm. ^{19}F NMR (377 MHz, $CDCl_3$): δ = –66.59 (s, 3 F) ppm. IR (neat): ν_{max} = 3696, 2967, 2217, 1595, 1337, 1112, 851, 746 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{13}H_8N_2F_3^+$ [M + H$^+$]: 249.0640; found: 249.0642.

This article differs from the e-First online version only in its layout; no content has been changed.