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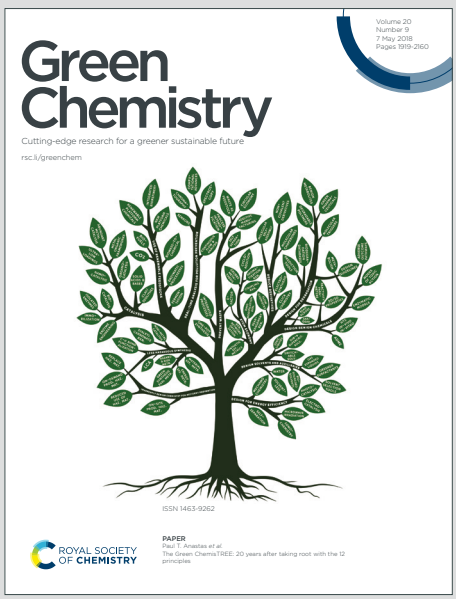

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COMMUNICATION

# Application of Cu(I)/TEMPO/$O_2$ Catalytic System for Aerobic Oxidative Dehydrogenative Aromatization of Pyrrolidines

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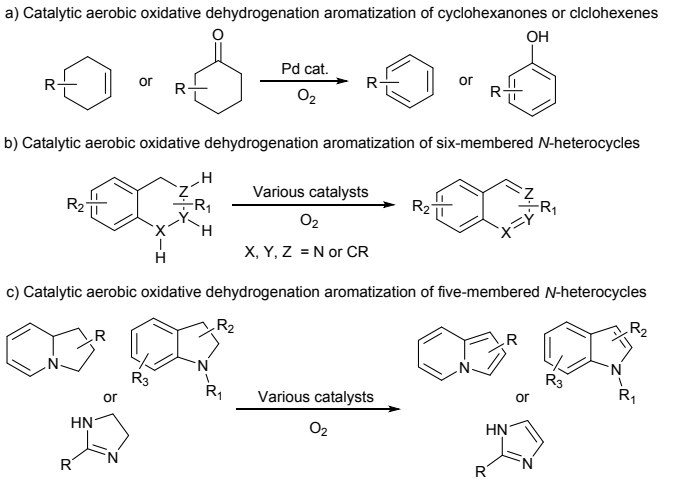
**A Cu(I)/TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy)-catalyzed aerobic oxidative dehydrogenative aromatization reaction of fully saturated pyrrolidines to synthesize multi-substituted pyrroles was developed for the first time. The use of non-precious metal catalyst, green oxidant and environmentally friendly solvent made the reaction more sustainable.**

Oxidative dehydrogenative aromatization protocols which could synthesize aromatic compounds from saturated cyclic compounds, have long attracted considerable attention from synthetic chemists because of high atom economy.[1] However, harsh reaction conditions or stoichiometric toxic oxidants are typically required in those protocols, which result in high cost and environmental pollution. Using cheap and readily available oxygen gas as the oxidant make oxidative dehydrogenative aromatization reactions more economical and environmentally friendly because water is the only by-product. In 2011, Stahl and co-workers reported a palladium catalyzed aerobic oxidative dehydrogenation reaction of cyclohexanone derivatives to produce phenols (Scheme 1a).[2a] Modified protocols successfully prepared poly-substituted aromatic rings from cyclohexanone and cyclohexene derivatives by the same group.[2] In addition, transition metal catalyzed aerobic oxidative dehydrogenative aromatization reaction of several partially saturated *N*-heterocycles, including six-membered *N*-heterocycles[3] (Scheme 1b) and five-membered *N*-heterocycles[4] (Scheme 1c) also had been reported. However, no effective methods for transition metal catalyzed aerobic oxidative dehydrogenative aromatization reactions of fully saturated cyclohexane derivatives or heterocycles under mild conditions emerged. These results may due to the fact that such reactions were both kinetic and thermodynamically unfavourable under conventional conditions.




**Scheme 1 Reported methods for transition metal catalyzed aerobic oxidative dehydrogenation aromatization of partially saturated cyclic compounds.**

Pyrroles are an important class of compounds that display a variety of biological activities, including anti-mycobacterial, anti-tumor, anti-fungal, anti-inflammatory, anti-tubercular and anti-HIV activity.[5] Many synthetic drugs, materials and dyes contain pyrrole units.[6] Therefore, the synthesis of pyrroles has long drawn much attention from synthetic chemists.[7] Stoichiometric amounts of 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (DDQ), *o*-iodoxybenzoic acid (IBX), manganese dioxide and benzoyl peroxide (BPO) have been reported to promote non-catalytic oxidative dehydrogenative aromatization of pyrrolidines (Scheme 2a).[8] However, those oxidants are often expensive or toxic, and the formation of stoichiometric amounts of by-products in the reaction limited their use. Although Rueping and co-workers reported a photo-redox dehydrogenative aromatization-sulfonylation reaction of pyrrolidines in 2018 (Scheme 2b),[9] the development of low-cost transition metal catalyzed aerobic oxidative dehydrogenative aromatization reactions of pyrrolidines is still remain challenge.

Cu(I)/nitroxyl/$O_2$ catalytic systems have emerged as the most versatile method to oxidize alcohols and amines.[10] However, to the best of our knowledge, it has never been used in oxidative dehydrogenative aromatization reaction of fully saturated cyclic compounds. Herein, we developed a CuCl/TEMPO (2,2,6,6-

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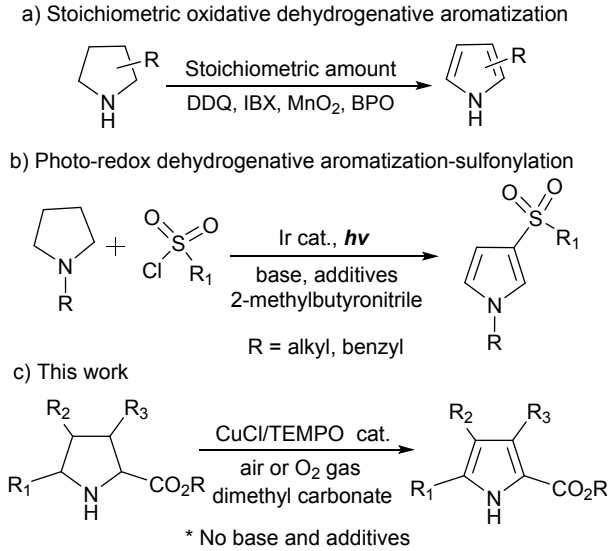
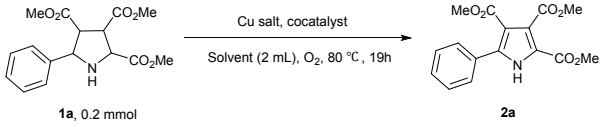
tetramethyl-1-piperidinyloxy) catalyzed aerobic oxidative dehydrogenative aromatization reaction of pyrrolidines (Scheme 2c).




**Scheme 2 Our and reported methods for oxidative dehydrogenative aromatization of pyrrolidines.**

Trimethyl 5-phenylpyrrolidine-2,3,4-tricarboxylate (**1a**) under $O_2$ atmosphere (balloon) was used to optimize the reaction conditions. First, several metal salts were investigated by using TEMPO as the co-catalyst and dimethyl carbonate (DMC) as the solvent at 80 °C (Table 1, entry 1–2). Successfully, trimethyl 5-phenyl-1*H*-pyrrole-2,3,4-tricarboxylate (**2a**) was produced in 40% yield with CuCl as the catalyst. Both CuCl and TEMPO were essential to this reaction (entry 3–4). Several TEMPO derivatives were proven as less efficient than TEMPO (entry 5–6). DMC was proved to be the best solvent (entry 2 and 7). We then optimized the amount of TEMPO (entry 8–10). When the catalyst loading of TEMPO was increased to 30 mol %, the yield of **2a** increased to 68% (entry 9). However, increasing the TEMPO loading to 50 mol % reduced the yield of **2a** to 44% (entry 10). Increasing the reaction concentration to 0.2 M and 0.3 M resulted in an increased product yield of 77% and 81%, respectively (entry 11–12). The optimized reaction conditions were established as: 0.30 mmol **1a** as the starting material, 0.03 mmol CuCl as the catalyst, 0.09 mmol TEMPO as the co-catalyst and 1.0 mL DMC as solvent at 80 °C for 19h under an $O_2$ atmosphere. **2a** was isolated in 76% yield under these standard reaction conditions (entry 12, **condition A**).

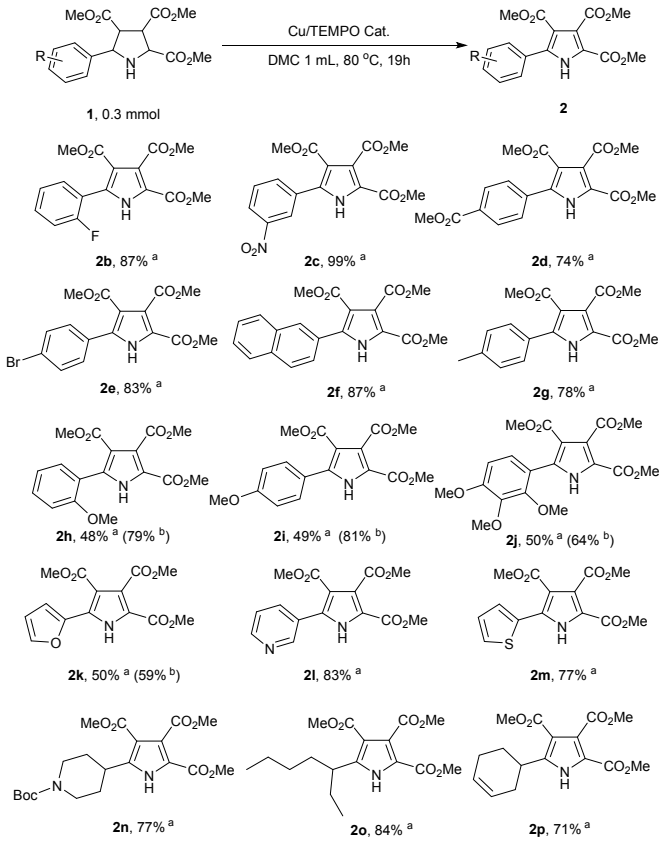
**Table 1 Optimization of reaction conditions**




| Entry | Cu salt (mol %) | Co-catalyst (mol %) | Solvent | Yield (%) [a] |
|---|---|---|---|---|
| 1 [b] | Other metal salts (10) | TEMPO (10) | DMC | 24-37 |
| 2 | CuCl (10) | TEMPO (10) | DMC | 40 |
| 3 | CuCl (10) | - | DMC | 0 |
| 4 | - | TEMPO (10) | DMC | trace |
| 5 | CuCl (10) | 4-OH-TEMPO (10) | DMC | 17 |
| 6 | CuCl (10) | 4-NHAc-TEMPO | DMC | 23 |
| 7 [c] | CuCl (10) | TEMPO (10) | Other solvents | trace-27 |
| 8 | CuCl (10) | TEMPO (20) | DMC | 64 |
| 9 | CuCl (10) | TEMPO (30) | DMC | 68 |
| 10 | CuCl (10) | TEMPO (50) | DMC | 44 |
| 11 [d] | CuCl (10) | TEMPO (30) | DMC | 77 |
| 12 [e] | CuCl (10) | TEMPO (30) | DMC | 81 (76 [f]) |

Reaction conditions: 10 % of metal salt and TEMPO derivatives as the catalyst, 0.2 mmol **1a**, 2 mL solvent, were stirred under $O_2$ (balloon) at 80 °C for 19h. [a] Yields were determined by $^1$H NMR using $CH_2Br_2$ as an internal standard. [b] Details in SI. [c] Including EtOH, MeCN, EtOAc and toluene. [d] 1.0 mL solvent. [e] 0.3 mmol of **1a** in 1.0 mL solvent. [f] Isolated yield.

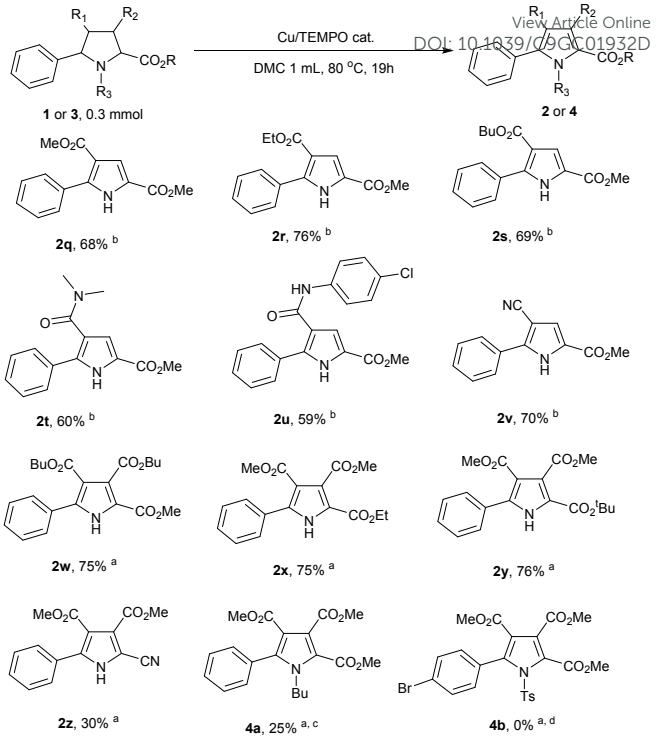
With the optimized conditions established, we studied the scope of pyrrolidines (Scheme 3). When the phenyl ring at the 5-position was substituted with electron-withdrawing groups (**1b–1e**), the corresponding pyrroles were isolated in good to excellent yields (74%–99%). Pyrrolidine substituted with 2-naphthyl at the 5-position also worked well and provided **2f** in 87% yield. When strong electron-donating groups were substituted on phenyl ring at the 5-position (**1h–1j**), the corresponding pyrroles were isolated in lower yields (48%–50%). These results may be because the electron-rich benzylic position was unstable under the copper catalytic aerobic oxidation process.[11] Further optimization of the reaction conditions revealed that under a milder condition (**condition B**: increased the amount of CuCl to 20 mol % and replaced $O_2$ with air, for details of optimization see the Supporting Information Table S2), the yields of the corresponding pyrroles (**2h–2j**) were significantly increased (64%–81%). Heterocycles, including pyridyl (**1l**), thienyl (**1m**) and *N*-Boc piperidinyl (**1n**) substituted at 5-position, were also tolerated and gave the corresponding products in good yield (77%–83%). Pyrrolidine substituted with an electron-rich furanyl (**1k**) gave pyrrole in 50% yield under condition A and 59% yield under the milder reaction condition B. Alkyl was also tolerated, the corresponding product (**2o**) was isolated in 84% yield. Surprisingly, when pyrrolidine was substituted with 3-cyclohexenyl at the 5-position, the corresponding pyrrole (**2p**) was afforded in 71% yield, and the double bond was unaffected under copper catalyzed aerobic oxidation conditions.




Isolated yield. [a] Condition A: CuCl 10%, TEMPO 30%, $O_2$. [b] Condition B: CuCl 20%,TEMPO 30%, air.

**Scheme 3 Substrate scope with different groups at 5-position of pyrrolidines.**

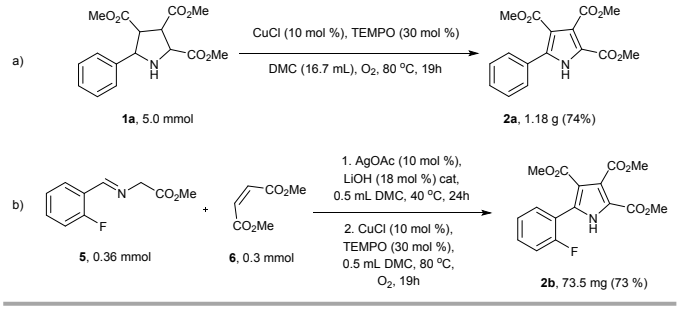
We then studied the substrate scope with different groups at other positions on pyrrolidine (Scheme 4). First, pyrrolidines with different groups at the 4-position, which include acrylates, acrylamides and acrylonitrile (**1q–1v**), did not react well under the optimized reaction condition A. The corresponding pyrroles, however, were produced smoothly under reaction condition B and isolated in yields from 59% to 76%. Notably, compared with *N,N*-dimethyl acrylamide (**1t**), no declined yield was observed when using *N*-(4-chlorophenyl)acrylamide (**1u**) as the starting material. When the methyl group at the 2-position was replaced by ethyl (**1x**) or steric *tert*-butyl (**1y**) groups, the yields of the corresponding pyrroles were unaffected. When methyl ester was replaced by a cyano group, the yield of **2z** dropped to 30%. The *p*-toluenesulfonyl protected pyrrolidine (**3b**) did not react under standard reaction conditions, but *N*-Bu pyrrolidine (**3a**) could produce corresponding pyrrole (**4a**) in 25% yield with 28% recovered **3a** under condition A.




Isolated yield. [a] Condition A: CuCl 10%, TEMPO 30%, $O_2$. [b] Condition B: CuCl 20%,TEMPO 30%, air. [c] **3a** was recovered in 28% yield. [d] **3b** was recovered in 98% yield.

**Scheme 4 Substrate scope of pyrrolidines.**

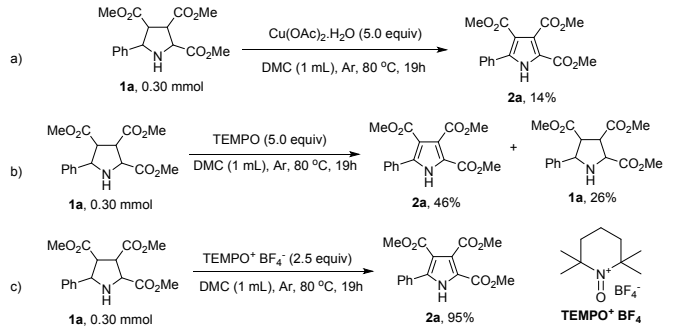
To demonstrate the practicality of the reaction, we successfully increased the reaction scale to gram-scale (Scheme 5a). Under condition A, 1.18 grams of **2a** was isolated, and the yield was comparable to yields from the small scale reactions. A successful one-pot method for the synthesis of pyrroles from Schiff bases and electron deficient alkenes was designed by combining our method with a previously reported 1,3-dipolar cycloaddition reaction (Scheme 5b).[8i] Pyrrole **3b** was isolated in 73% yield, which provides a highly efficient method from simple and readily available starting materials to prepare multi-substituted pyrroles.




**Sheme 5 Gram-scale reaction and one-pot reaction for synthesis of pyrroles.**

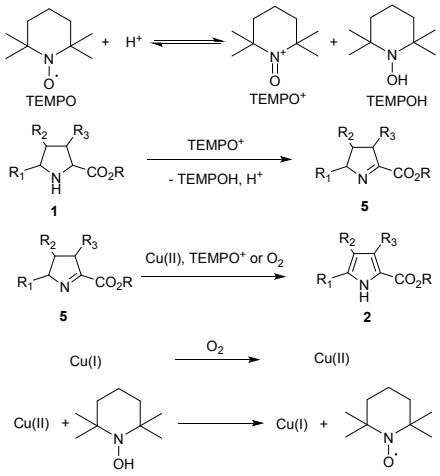
To reveal the reaction mechanism, a series of control experiments were conducted. 5.0 equivalent copper acetate monohydrate, TEMPO and 2.5 equivalent 2,2,6,6-tetramethyl-1-oxopiperidin-1-ium fluoroborate ($TEMPO^+BF_4^-$)[12] were reacted with **1a** under argon atmosphere respectively. Pyrrole **2a** was isolated in 14% yield and no **1a** was recovered using copper acetate as the

oxidant (Scheme 6a). Pyrrole **2a** was isolated in 46% yield and **1a** was recovered in 26% yield using TEMPO as the oxidant (Scheme 6b). Pyrrole **2a** was isolated in 95% yield and no **1a** was recovered using $TEMPO^+BF_4^-$ as the oxidant (Scheme 6c).




**Scheme 6 The control experiments.**

Base on above results and previous results, 2,2,6,6-tetramethyl-1-oxopiperidin-1-ium ($TEMPO^+$) was proven to be an active oxidant and the copper catalyst could help to regenerate the oxidant under oxygen gas. Therefore, the suggested mechanism was show in scheme 7. First, TEMPO was going disproportionation to generate TEMPOH (2,2,6,6-tetramethylpiperidin-1-ol) and $TEMPO^+$.[13] Then, pyrrolidines was oxidized by $TEMPO^+$ to form imine intermediate (**5**).[14] Next, intermediate **5** was oxidized by copper(II), $TEMPO^+$ or oxygen gas to form pyrrole product. Copper(I) was oxidized by oxygen gas to generate copper(II). At last, copper(II) reacted with TEMPOH to regenerate TEMPO and copper(I).




**Scheme 7 Plausible mechanism.**

## Conclusions

In summary, a Cu(I)/TEMPO catalyzed aerobic oxidative dehydrogenative aromatization reaction to synthesize multi-substituted pyrroles from pyrrolidines has been developed. This reaction tolerated functional groups well and was easy to conduct at gram scale. Using cheap and readily available oxygen as the oxidant and green solvents made this transformation environmentally friendly.

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## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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