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Mild and ambient annulations for pyrrole synthesis from amines and arylacetaldehydes

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**A mild and ambient pyrrole synthesis via copper-catalyzed aerobic cyclization of alkylamines and arylacetaldehydes is described. This method provided alternative access to a range of 1,3,4-trisubstituted pyrroles under environmentally friendly reaction conditions.**

Oxidative transformation is a fundamental and highly significant process in organic reactions. With the consideration of sustainable development, mild C-H functionalization using air, i.e. molecular oxygen, as the oxidant is an ideal manipulation in organic synthesis since it is an environmentally friendly oxidant and water is the sole byproduct.[1] However, such a composition faces big challenges such as the high activation energy of molecular oxygen.[2] Copper catalysts feature high performance in the oxidative synthesis with molecular oxygen due to their abundant valence states and the affinity with molecular oxygen, which provides those reactions with considerable feasibility under mild conditions.[3] A classic example is the copper-catalyzed aerobic homo-coupling of terminal alkynes, i.e. Glaser–Hay reactions, which were widely applied in synthetic chemistry and material science.[4] In the past decade, a wide range of copper-catalyzed aerobic strategies were implemented for ambient C-C and C-heteroatom bond formation to provide various functionalized products.[5] In despite of the progress, the activation of molecular oxygen and its application in oxidative organic synthesis, particularly under ambient conditions, remain a significant target for chemists.

Pyrroles represent one of the most important classes of heterocyclic compounds which were found in a large number of natural and biologically active compounds, exhibiting a range of pharmacological activities such as antitumor, anti-inflammatory, and antibiotic activities.[6] Therefore, the synthetic methodology of substituted pyrroles is still a hot research topic in the area of organic chemistry. Beyond the classical Paal−Knorr, Huisgen, and Hantzsch processes,[7] in the past decades, various approaches have been developed for facile synthesis of substituted pyrroles via catalytic cyclization from easily available precursors.[8] Amines and aldehydes are common and commercially available reagents, which were frequently employed to construct heterocycles, such as pyridines,[9] azoles,[10] and pyrroles.[11] For pyrroles, for example, Jia and co-workers reported AgOAc-mediated cyclization of aldehydes and anilines,[11b] preparing a series of symmetrically substituted pyrroles with the assistance of stoichiometric silver salt and base. In 2013, Huang and Yan designed an I2-catalyzed synthesis of substituted pyrroles from α-amino carbonyl compounds and aldehydes.[11c] Jiao and co-workers also developed differently disubstituted pyrrole synthesis switched by copper and nickel catalysts starting from aryl acetaldehydes and vinyl azides.[11d] In addition to previous work of Chichibabin-type pyridine synthesis from aryl acetaldehydes and alkyl amines under Lewis acid catalysis (Scheme 1a),[9d] in this paper, we describe a mild synthesis of substituted pyrroles from aryl acetaldehydes and alkyl amines under copper-catalyzed aerobic conditions (Scheme 1b). This work features advantages including facile manipulation, high atom-economy, environmentally friendly water as the sole byproduct, and moreover providing an alternative thinking for mild activation of molecular oxygen under copper catalysis.
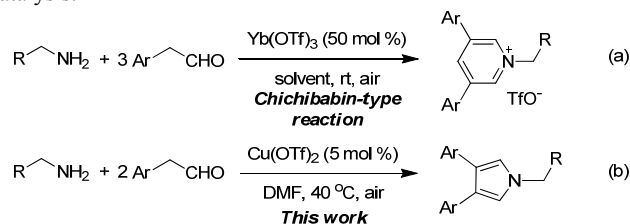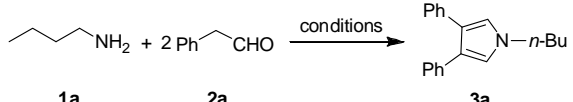

Scheme 1 cyclization of aryl acetaldehydes and alkyl amines under ambient condtions.

Initially, we chose *n*-butylamine (**1a**) and phenylacetaldehyde (**2a**) as the model system to optimize the reaction conditions (Table 1). It was found from the first experiment that the reaction performed under Cu(OAc)2 catalysis in DMF at 80 °C for 12 h only gave a trace of the target product **3a** (Table 1, entry 1). However, this result encouraged us to further screen different copper salts, such as

Cu(TFA)$_2$, CuCl$_2$, CuBr, and CuI. These copper catalysts all worked for this cyclization reaction (Table 1, entries 2-5), howbeit giving low yields of the pyrrole (8-27%). Surprisingly, when Cu(OTf)$_2$, a high-Lewis-acidic copper catalyst, was employed, the yield of this transformation was significantly enhanced to 64% (Table 1, entry 6). The reaction temperature was found critical for the productivity (Table 1, entries 6-9), and the reaction at 40 ^{o}C in a prolonged reaction time (24 h) furnished the highest yield of **3a** (Table 1, entry 9, 95%). Notably, decreasing the amount of amine substrate **1a** to 0.6 equivalents led to a slight drop in the yield (Table 1, entry 10). We also conducted this reaction under an oxygen atmosphere. However, a decreased yield was obtained (Table 1, entry 11). The optimal catalyst loading was then determined to be 5 mol% (Table 1, entries 12-13). Finally, it was found that the reaction in the absence of copper catalyst or under argon atmosphere did not work.
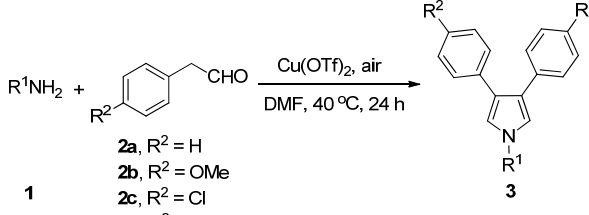
Table 1 Optimization of reaction conditions^a

Entry	[Cu] catalyst (mol %)	Temp (^{o}C)	Yield^b
1	Cu(OAc)$_2$ (5)	80	trace
2	Cu(TFA)$_2$ (5)	80	12
3	CuCl$_2$ (5)	80	27
4	CuBr (5)	80	20
5	CuI (5)	80	8
6	Cu(OTf)$_2$ (5)	80	64
7	Cu(OTf)$_2$ (5)	60	79
8	Cu(OTf)$_2$ (5)	50	82
9^c	Cu(OTf)$_2$ (5)	40	95
10^{c,d}	Cu(OTf)$_2$ (5)	40	93 (82)
11^{c,e}	Cu(OTf)$_2$ (5)	40	80
12^c	Cu(OTf)$_2$ (7.5)	40	81
13^c	Cu(OTf)$_2$ (2)	40	75
14^f	—	40	ND
15^g	Cu(OTf)$_2$ (5)	40	trace
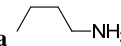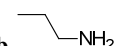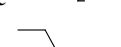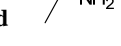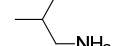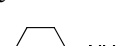
^{a} The reactions were performed with 0.5 mmol of **1a**, 0.5 mmol of **2a** in 1 mL of DMF under air for 12 h. ^{b} GC yield based on **2a** is presented. ^{c} The reactions were performed for 24 h. ^{d} 0.3 mmol of **1a** (0.6 equiv.) were used, with isolated yield in the parentheses. ^{e} The reaction was performed under 1 atm of O$_2$. ^{f} The reaction was performed in the absence of copper catalyst. ND means not detected. ^{g} The reaction was performed under an argon atmosphere.

Synthetically considering the yielding and the issue of reaction atom-economy, 0.6 equivalents of amines were used as the optimal dosage for the reaction. Thus the optimal conditions of this cyclization consisted of amine (0.6 equiv.), aromatic acetaldehyde (1.0 equiv.)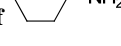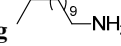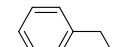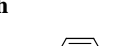, and Cu(OTf)$_2$ (5 mol%) in DMF (0.5 M) at 40 ^{o}C under air for 24 h. Next, we explored the generality and the scope of this copper-catalyzed aerobic cyclization under the optimized reaction

conditions (Table 2). All aliphatic amines employed (**1a-1g**) reacted well with phenylacetaldehyde to give the corresponding pyrroles **3a-3g** in good yields (Table 2, entries 1-7), with no obvious steric effect of the alkyl groups. Aromatic ethylamines, such as **1h**, **1i**, and **1j**, also efficiently afforded pyrroles **3h**, **3i**, and **3j**, respectively (Table 2, entries 8-10). Then benzyl amine **1k** was subjected to this reaction, delivering the expected N-benzyl pyrrole **3k** in moderate yield (Table 2, entry 11). Phenylacetaldehyde derivatives with methoxyl (**2b**), chlorin (**2c**), and tert-butyl (**2d**) on the *para* position of the benzene ring worked smoothly with amines to afford the corresponding products in good yields (Table 2, entries 12-14). However, 2-substituted aromatic acetaldehydes or heteroaromatic acetaldehydes with furyl or thienyl motif were all out of work in this system.

Table 2 Preparation of 1,3,4-trisubstituted pyrroles^a

2a, R^2 = H
2b, R^2 = OMe
2c, R^2 = Cl
2d, R^2 = t-Bu

Entry	1 (Amine)	2	Product	Yield
1	**1a**	**2a**	**3a**	82
2	**1b**	**2a**	**3b**	82
3	**1c**	**2a**	**3c**	68
4	**1d**	**2a**	**3d**	77
5	**1e**	**2a**	**3e**	80
6	**1f**	**2a**	**3f**	85
7	**1g**	**2a**	**3g**	91
8	**1h**	**2a**	**3h**	75
9	**1i**	**2a**	**3i**	72
10	**1j**	**2a**	**3j**	68
11	**1k**	**2a**	**3k**	65
12	**1b**	**2b**	**3l**	80
13	**1b**	**2c**	**3m**	71
14	**1c**	**2d**	**3n**	82

a The reactions were performed with 0.3 mmol of **1**, 0.5 mmol of **2a**, and 0.025 mmol of Cu(OTf)$_2$ in 1 mL of DMF under air at 40 ^{o}C for 24 h. Isolated yields were given.

Unfortunately, the treatment of aliphatic amine **1a** with aliphatic aldehyde **2e** [eqn (1)], as well as the reaction of phenylacetaldehyde **2a** and arylamine **1l** [eqn (2)], was documented to be invalidated in this copper/oxygen-based system. An unexpected result was obtained when arylamine **1l** was combined with aliphatic aldehyde **2e** into the present system, where 2,3-dialkyl quinoline **4** was given in excellent yield [eqn (3)]. We also employed phenylhydrazine (**1m**) and benzenesulfonyl hydrazide (**1n**) as the substrate in the present system [eqn (4)]. The corresponding products **3o** and **3p** were detected by GC-MS in 55% and 48% yield, respectively. However, no purified products could be obtained after flash column chromatography even with basic alumina, which was probably due to the instability of this kind of compounds. A further transformation of the resultant 1,3,4-trisubstituted pyrroles was smoothly realized. When pyrrole **3h** was treated with stoichiometric *N*-bromosuccinimide (NBS), bromized product **5** was highly efficiently obtained in a full conversion [eqn (5)]. Finally, to gather informations of the reaction mechanism, we used 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-tert-butyl-4-methylphenol (BHT) as the radical traps to conduct the reaction. No desired product **3a** was observed in both cases [eqn (6)], which indicates this reaction probably undergo a radical pathway.
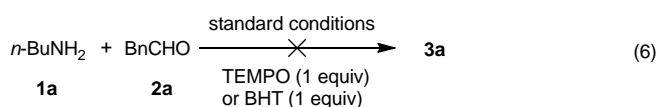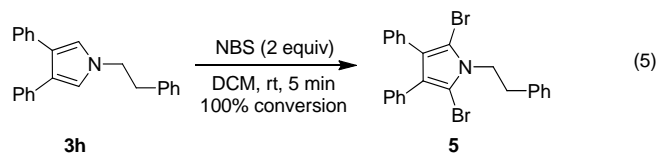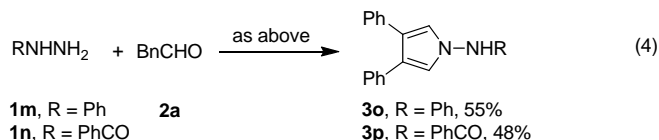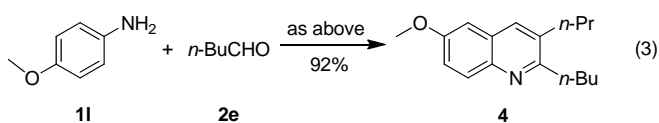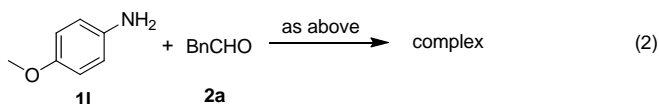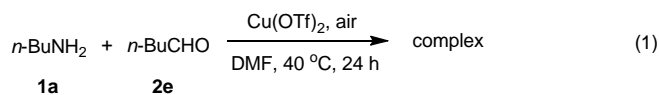
Based on above experimental observation and previous works involving homodimerization of enamines, a plausible mechanism was proposed for this copper-catalyzed aerobic cyclization (Scheme 2). The condensation of aldehydes and amines forms imine **A**, which isomerizes to enamine **B**. Then copper-mediated single-electron transfer furnishes radical intermediate **C**. Homodimerization of the radical gives **D**, which can also be formed through the addition of **C** to enamine **B** and subsequent single electron oxidation via the

intermediate **E**. Intermolecular nucleophilic attack/cyclization and subsequent amine elimination result in the final pyrroles. The liberative copper(I) can be oxidized to catalytically active copper(II) by oxygen in air. Notably, we deem Cu(OTf)$_2$ irreplaceable due to playing a dual role of transition metal and Lewis acid which could assist both processes of condensation and amine elimination.
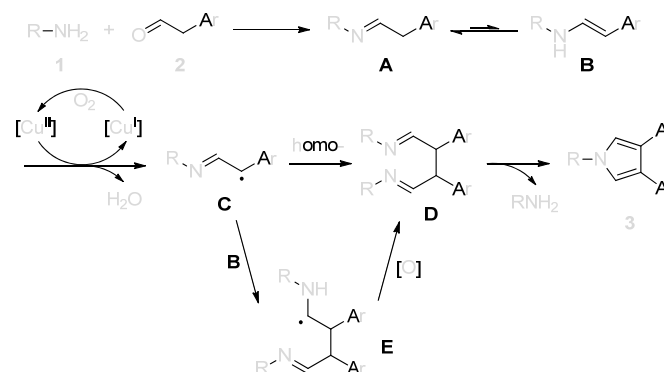
Scheme 2 Plausible reaction mechanism for this copper-catalyzed aerobic cyclization.

Conclusions

In summary, a facile ambient copper-catalyzed aerobic system has been developed for the synthesis of substituted pyrroles. Aromatic acetaldehydes and alkyl amines have been documented to work well in present system, delivering a range of 1,3,4-trisubstituted pyrroles in good to excellent yields. Mechanistically, a cascade process involving aldehyde-amine condensation and single-electron-oxidative homodimerization was proposed. This methodology features advantages including green oxidant, mild conditions, and high atom-economy.

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Notes and references

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