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Direct use of dioxygen as an oxygen source: catalytic oxidative synthesis of amides†

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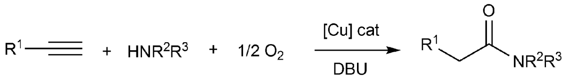
The first transition-metal-catalyzed direct oxidative synthesis of amides by using dioxygen as an oxygen source has been developed under mild conditions, in which DBU was used as the key additive. The present methodology, which utilizes dioxygen as an oxidant and oxygen source and cheap copper salts as catalysts, opens up an interesting and attractive avenue for the synthesis of amide functionality.

The synthesis of diverse oxygen-containing blocks is one of the most fundamental and significant subjects in organic chemistry. From the viewpoint of green and sustainable chemistry, employing dioxygen as the oxidant and oxygen source for functionalization of organic substrates represents one of the most ideal methodologies for producing oxygenated compounds. During the past several decades, considerable efforts have been made in this area[1] and some important oxygen-containing compounds such as alcohols, aldehydes, ketones, carboxylic acids, and epoxides have been successfully obtained through the catalytic oxidation reaction using dioxygen. Nevertheless, there is still a great demand for the development of a new and selective aerobic oxidation system to afford other important and useful oxygenated building blocks.

As an extremely valuable oxygen-containing functional group, the amide functionality strongly attracts synthetic pursuit of chemists in both academic and industrial communities, since it is one of the most vital structural motifs in life and materials sciences.[2] The direct incorporation of an oxygen atom from dioxygen into organic substrates for the formation of amide bonds has been observed in some biological oxygenase systems.[3] For example, cytochrome P450 catalyzed oxidative biotransformation of amidoximes and nitriles to the corresponding amides in liver microsomes.[3b,c] Although biomimetic studies of such enzymes catalyzed oxidative amidation reactions using dioxygen have been investigated, it is still challenging to develop non-biomimetic aerobic oxidation systems employing simple metal salts as catalysts to conveniently access amides. Herein, we present a novel copper-catalyzed direct oxidative synthesis of amides from alkynes, amines, and dioxygen under mild conditions (eqn (1)), in which DBU was used as the key additive. To the best of our knowledge, this is the first example of transition-metal-catalyzed direct oxidative synthesis of amides from simple and readily available materials by employing O_2 as the oxidant and oxygen source.[4]



(1)

In general, traditional approaches for amide synthesis rely heavily on the use of activated carboxylic acids and amines, which often require stoichiometric amounts of coupling reagents and produce toxic chemical waste.[5] Recently, catalytic oxidative methods have become a powerful tool for the construction of amide complexes, in which oxygen atoms of amides generally originate from oxone/H_2O_2[6] or oxygen-containing carbonyl precursors including aldehydes[7] and alcohols.[8] Nevertheless, such well developed oxidative reactions usually require stoichiometric oxidants such as TBHP[7a,b] and oxone,[6,7c] expensive or relatively complex transition metal catalysts such as Ru,[8a–c] Rh,[7d,8d] and Mn[6] complexes. The present methodology, which utilizes dioxygen as an oxidant and oxygen source and cheap copper salts as catalysts, opens up a new and attractive window for the synthesis of amide functionality.

Initially, under an oxygen atmosphere, the reaction of phenylacetylene **1a** with piperidine **2a** was performed to examine the catalytic activity of various transition metal complexes including Ru, Rh, Pd, Ti, Au, Ag, Cu, Fe, Ni, and Zr salts. As shown in Table 1, among those metal catalysts examined (entries 1–3), copper salts especially CuBr was found to be able to catalyze the formation of amide **3aa**, albeit in low yield (entry 3). Preliminary exploration using CuBr as catalyst led to a discovery that the base was the critical additive for improving this amidation reaction. Among various bases examined, DBU turned out to be the best choice, while others such as Cs_2CO_3, Na_2CO_3, DBN, Et_3N, $^iPr_2NEt$, and pyridine were less effective (entries 4–7). After an extensive screening of the reaction parameters (see Table 1 and ESI†), the best yield of **3aa** (68%) was obtained by employing phenylacetylene (2.5 mmol), piperidine (0.5 mmol), CuBr (5 mol%), and DBU (0.6 mmol) in THF at 55 °C (entry 7). The high loading of alkynes might be caused by the side reaction of the dimerization of alkynes (Glaser reaction), which easily occurred with copper catalyzed reactions of alkynes with amines in the

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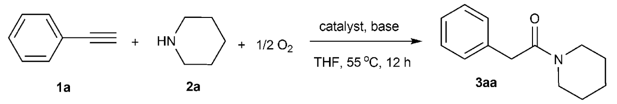
Table 1 Oxidative amide synthesis under various conditions[a]



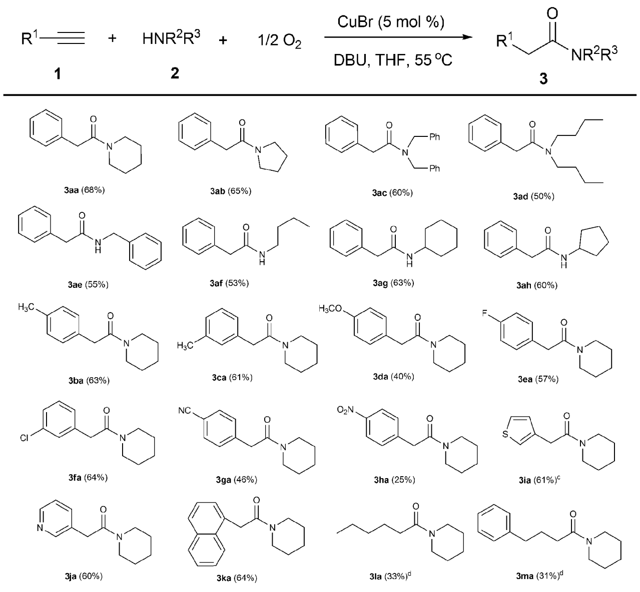
Entry	Catalyst	Yield[b] (%)
1	$RuCl_3$, or $RhCl_3$, or $Pd(OAc)_2$, or $AuBr_3$, or AgOTf, or $NiCl_2$, or $Ti(O\textit{i}Pr)_4$, or $(C_5H_5)_2ZrCl_2$, or $FeBr_3$	0[c]
2	CuI, or CuCl, or $CuCl_2$, or $CuBr_2$, or $Cu(OTf)_2$	Trace
3	CuBr	4
4	CuBr/Na_2CO_3, or Et_3N, or $^iPr_2NEt$, or pyridine	< 5
5	CuBr/Cs_2CO_3	21
6	CuBr/DBN	55
7	**CuBr/DBU**	**68**
8	CuBr/DBU, air	35
9	CuBr/DBU, N_2	0
10	–/DBU	0

[a] Reaction conditions: **1a** (2.5 mmol), **2a** (0.5 mmol), catalyst (5 mol%), base (0.6 mmol except entries 1–3), THF (1.0 mL), O_2 (balloon). [b] Isolated yields based on **2a**. [c] The same results were obtained in the presence of DBU (0.6 mmol).

presence of a base and dioxygen.[9] This amidation reaction could also proceed smoothly under the air atmosphere (entry 8). No conversion was observed in the absence of copper catalyst or O_2 (entries 9 and 10).

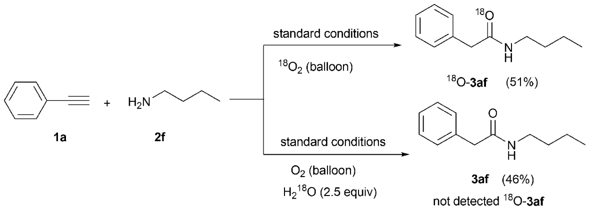
Under the optimized conditions, the scope of this reaction was tested with various combinations of alkynes and amines (Table 2). In general, when **1a** was employed, both primary and secondary amines (including cyclic and acyclic amines) afforded the corresponding amides **3aa–3ah** in moderate to good yields. With respect to alkynes, both electron-rich and electron-deficient aromatic alkynes in our cases could be transformed into the desired products (**3ba–3ha**). In addition, heteroaromatic alkynes such as 3-ethynylthiophene and 3-ethynylpyridine were also compatible with this reaction, providing the corresponding products in 61% and 60% yields, respectively (**3ia** and **3ja**). 1-Ethynylnaphthalene could also be used in the reaction to give the expected product **3ka** in 64% yield. Nevertheless, when aliphatic alkynes such as 1-hexyne and 4-phenyl-1-butyne were used as the substrates, the corresponding products were obtained in relatively low yields (**3la** and **3ma**).

Table 2 Results for the reaction of the oxidative amidation of alkynes[a,b]



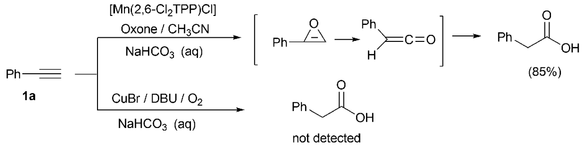
[a] Reaction conditions: **1** (2.5 mmol), **2** (0.5 mmol), CuBr (5 mol%), DBU (0.6 mmol), THF (1.0 mL), 4–24 h, O_2 (balloon). [b] Isolated yields based on **2**. [c] DBN (0.6 mmol). [d] Neat conditions, 24 h.

In order to obtain clear mechanistic insight into the function of molecular oxygen, labeling experiments using $^{18}O_2$ and $H_2{}^{18}O$ were conducted in the reaction of phenylacetylene **1a** with *n*-butylamine **2f**, respectively (eqn (2)), and the results showed that the oxygen atom of the amide originated from molecular oxygen (HRMS, see ESI†).



(2)

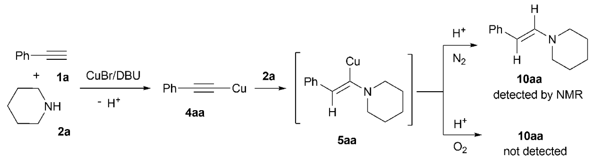
Oxirene and ketene were proposed as the key intermediates in the oxidative amidation of alkynes using oxone by Che, and the corresponding mechanism was proved by the conversion of phenylacetylene to phenylacetic acid under aqueous $NaHCO_3$ conditions (eqn (3)).[6] However, in our standard reaction conditions, when amine was replaced with aqueous $NaHCO_3$, no conversion of phenylacetylene to phenylacetic acid was observed (eqn (3)). So we considered that the oxirene and ketene intermediates might not be involved in this oxidation process.



(3)

The exact mechanism of the direct oxidative amidation of alkynes using dioxygen is unclear at the present stage. However, related experimental phenomena and previous reports[10–14] provide some helpful information for our tentative understanding of this process.

Firstly, it is known that phenylethynyl-copper(I) species as a precipitate could be obtained from the reaction of phenylacetylene with copper salts in the presence of a base.[10] In the present reaction system of phenylacetylene **1a** and piperidine **2a**, a yellow insoluble precipitate of the phenylethynyl-copper(I) was formed in the absence of DBU,[11] which might be explained by the weak base effect of **2a**. After DBU was added to the above reaction mixture, this precipitate of the phenylethynyl–copper(I) completely dissolved and the corresponding product **3aa** could be detected by TLC (Thin-layer Chromatography). Based on these observations and previous studies about using DBU as ligand in other copper catalyzed reactions,[12] we assumed that in our reaction system, DBU might act not only as an organic strong base to promote the generation of copper acetylides, but also as a ligand to chelate with copper(I) acetylide and enhance the solubility and reactivity of copper species.

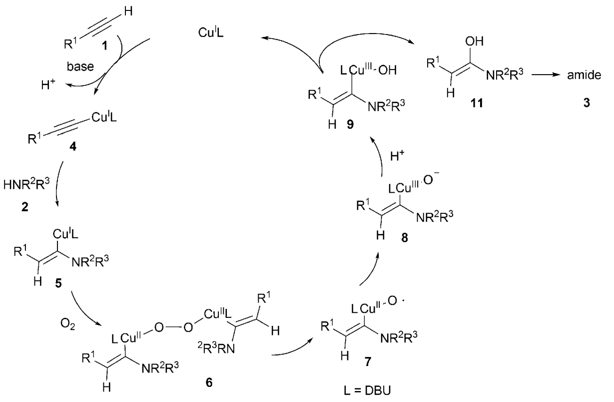


(4)

Subsequently, when the reaction of **1a** with **2a** was conducted in the absence of dioxygen, enamine intermediate **10aa** was detected by NMR (see ESI†) (eqn (4)). Nevertheless, enamine intermediate **10aa** could not be detected in the presence of dioxygen (eqn (4)). According to the general process of the anti-Markovnikov hydroamination of alkyne,[9d,13] we envisioned that α-aminovinylcopper(I) complex **5aa**, the hydroamination product of copper acetylide **4aa**, might be involved in the present reaction system. In the absence of dioxygen, **5aa** underwent protonation to afford enamine intermediate **10aa**, which was proved by ^{1}H NMR. On the basis of the growing amount of information about copper–dioxygen reactivity,[14,15] we speculated that **5aa** might react more readily with dioxygen to generate the corresponding copper–oxygen complex under an oxygen atmosphere, which would lead to the formation of the C–O bond in subsequent reactions.[14d]

Based on the above information and previous studies,[10–16] we propose a postulated reaction pathway shown in Scheme 1. The LCu(I)-acetylide species **4** (L = DBU) was formed by the reaction of the Cu(I) species with alkyne in the presence of DBU and amine. Then, the reaction of the acetylide species with amine would lead to the formation of the key intermediate α-aminovinyl–Cu(I) complex **5**. Subsequently, complex **5** was quickly oxygenated by dioxygen to form more active μ-peroxo dicopper(II) complex **6**,[14] which underwent the O–O bond cleavage,[15] single electron transfer,[16] protonation, followed by reductive elimination of copper species to deliver the corresponding α-aminoenol complex **11** and Cu(I) species. Finally, the desired amide **3** was generated by the isomerization of **11**.

In conclusion, we have developed the first transition-metal-catalyzed direct oxidative synthesis of amides by employing O_2 as the oxidant and oxygen source. In this process, anti-Markovnikov hydroamination of alkyne and subsequent oxidation by copper activated dioxygen into the resulting amide could be accomplished in a single operation. The present methodology opens up an interesting and attractive avenue for the synthesis of amide functionality due to the following features: easily available materials, cheap catalyst, and environmentally benign oxygen source. Studies of the detailed mechanism of this process and its application are ongoing.



Scheme 1 Postulated reaction pathway.

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