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Selective C-C Bond Cleavage of Amides Fused to 8-Aminoquinoline Group Controlled by Catalyst and Oxidant

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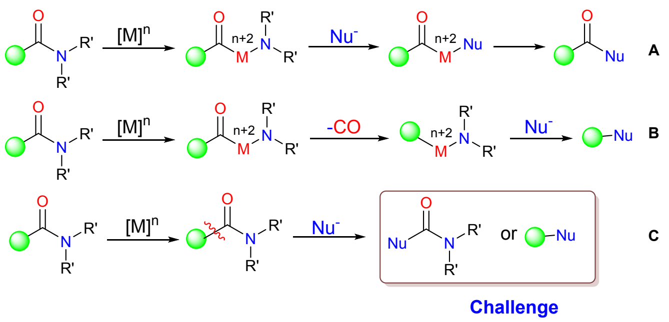
Herein, copper-catalyzed direct C-C bond cleavage of amides fused to 8-aminoquinoline as a directing group to form urea in the presence of amines and dioxygen is reported. Compare to the previous C-H aminations of amides by C-H activation, this reaction presents a catalyst and oxidant controlled C-C bond cleavage strategy that enables amidation through a radical process. $CuBr/Ag_2CO_3/O_2$ showes the best catalytic result in 150 °C. A series of aryl and alkyl amides were compatible with this transformation. Notably, this method provided an access to cyclohexanone, one of the most important industrial materials. The pathway of this reaction was investigated.

Introduction

Transition-metal-catalysed amide transformations through C-N or C-C bond cleavage have emerged as a powerful tool for the synthesis of organic molecules, as amides are common in nature, and their conversions are important.[1] Therefore, numerous efforts have been devoted to such reactions, including the establishment of new catalytic systems and, studies of the reaction mechanisms.[2] Among these, the nickel-(0) catalysts developed by Garg and the palladium-(II) complexes disclosed by Szostak can efficiently cleave the C-N bonds of amides.[3, 4] Mechanistically, the transition-metal-catalysed amide transformation was found to generally involve metal insertion into the amide N-C bond (oxidative addition) followed by transmetallation and elimination to form an acyl compound, such as a ketone, an amide or an ester (Scheme 1, A).[5, 6, 7, 8] In addition, some compounds subsequently undergo decarbonylation of the acyl-metal intermediate to realize C-C(=O) bond cleavage, which delivers aryl derivatives or alkenes (Scheme 1, B).[9, 10] However, the direct C(sp^2 or sp^3)-C (=O) bond cleavage of amides instead of by C-N bond cleavage first remains a challenge, because that oxidative addition to the metal catalyst is more difficult than that of the C(O)-N bond (Scheme 1, C).[11]



Scheme 1 Pathways of amide conversion

On the other hand, even though works on C−C(=O) bond cleavage of acyl compounds and their derivatives have significantly increase in the past decades, direct C−C(O) bond cleavage is still largely confined to ketones because compared to acids, esters, amides and other acyl compounds, ketones have no other sites that are more active toward the addition of the catalyst.[12] In this context, Jiao reported elegant works on the copper-catalyzed aerobic oxidative C-C bond cleavage of unstrained ketones to realize amidation and esterification.[13] Bi and Wang independently reported copper-catalyzed transformations of methyl ketones into aldehydes or other ketones.[14] Jiang and Paine independently found that α-hydroxy ketones could be converted to acids or esters.[15]

Recently, 8-aminoquinolinebenzamides have captured substantial attention from the organic chemistry community because these compounds can be directly installed with a variety of functional groups at the ortho position of amide groups via transition-metal-catalyzed C-H activation. This type of reaction was considered proceed via a stable, five-membered-ring carbon-metal species followed by nucleophilic coordination

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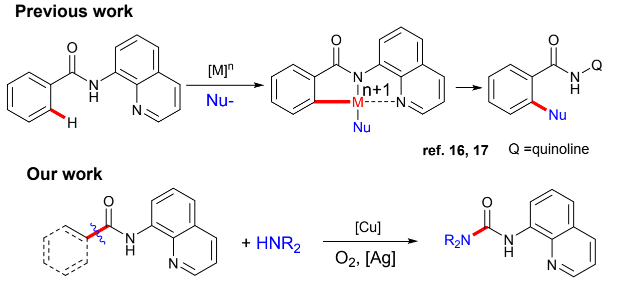
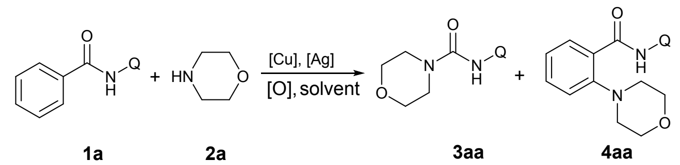


Scheme 2 The conversion of 8-aminoquinolinebenzamide

and reductive elimination to afford for the desired products.[16] When amines were employed as the nucleophiles, the selective C-H amination reaction was carried out under oxidative or electrochemical conditions.[17] However, to date, the C-C(=O) bond cleavage of 8-aminoquinolinebenzamides has not been reported. Herein, an unconventional copper-catalysed C-C(=O) bond cleavage of 8-aminoquinolineamides in the presence of secondary amines is reported (Scheme 2).

Table 1 Optimization of the reaction conditions [a]



entry	[Cu]	[Ag]	solvent	**3**:**4** yield %[b]
1	Cu_2O	Ag_2CO_3	toluene	35/36
2	CuBr	Ag_2CO_3	toluene	60/trace
3	$Cu(OAc)_2$	Ag_2CO_3	toluene	trace/59
4	-	Ag_2CO_3	toluene	-
5	CuBr	-	toluene	25/trace
6	CuBr	Ag_2CO_3	tol/diox (1:1)	74/trace
7[c]	CuBr	Ag_2CO_3	tol/diox (1:1)	trace/57

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.9 mmol), [Cu] 50 mol%, [Ag] (200 mol%), solvent solvent (2.0 ml), O_2, 150 °C, 12 h; [b] Isolated yield; [c] Under air instead of O_2.

We initiated our investigation with the reaction of **1a** and **2a** in toluene to identify the optimal reaction conditions. Fortunately, when the reaction was conducted with Cu_2O (0.5 equiv.) as the catalyst and Ag_2CO_3 (2.0 equiv.) as an additive at 150 °C in an O_2 atmosphere for 12 h, we found that urea **3a** was produced in 35% yield along with C-H amination product **4a** in 36% yield, and the benzene fragment was transformed to an unknown mixture (Table1, entry 1). Encouraged by this, various Cu salts were screened. When CuBr was employed in the reaction, the selectivity of the reaction was dramatically increased, furnishing **3a** in 60% yield with a trace amount of **4a** (Table 1, entry 2). In contrast, in the presence of $Cu(OAc)_2$, the reaction afforded **4a** in 59% yield with a trace amount of **3a** (entry 3). Moreover, in the absence of a Cu source, neither **3a** nor **4a** were generated (entry 4). Notably, the Ag salt played an important role in this transformation. When Ag_2CO_3 was omitted from the reaction, desired product **3a** was obtained in 25% yield with only a trace amount of **4a,** and silver mirror was found (entry 5). (Please see SI). When a mixture of 1, 4-Dioxane (1 mL) and toluene (1 mL) was used in this reaction, the yield of desired product **3a** was increased to 74%, yield and no **4a** was found (entry 6). When air was used in place of O_2, no C-C bond cleavage product was observed, and only C-H amination product **4a** was isolated respectively, suggesting that O_2 is essential for this reaction (entry 7 and see the SI).

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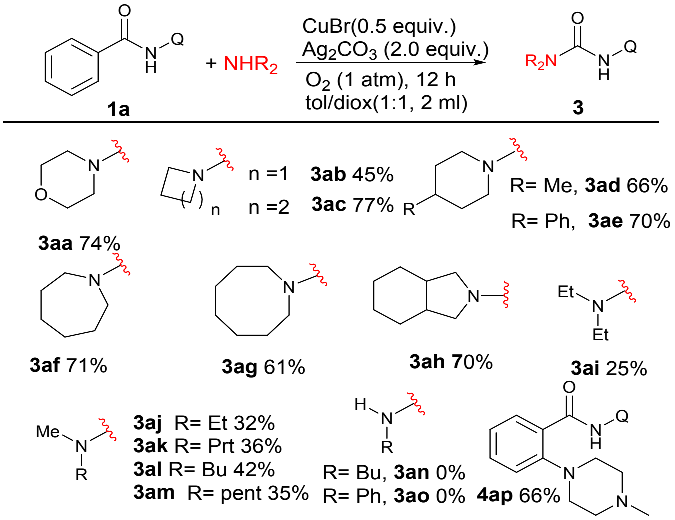


Figure 1 The scope of amines

Upon establishing the optimized reaction conditions, the amine scope was investigated. As shown in Figure 1, cyclic amines such as four-membered azetidine and pyrrolidine were compatible with this transformation, giving the desired product in 45% and 77% yields (**3ab**, **3ac**). When 4-methylpiperidine and 4-phenylpiperidine were subjected to the reaction, the desired products were obtained in 66% and 70% yields, respectively (**3ad**, **3ae**). Furthermore, amines with larger rings, such as azepane and azocane, were also tolerated (**3af** and **3ag**). In addition, octahydro-1H-isoindole delivered the desired product in 70% yield (**3ah**). Acyclic secondary amines are less reactive than cyclic secondary amines. This may be due to steric effects (**3ai**). Amines with less steric hindrance, such as amines with methyl groups, were subjected to this procedure, and the C-C cleavage products were isolated in 32% to 42% yields respectively (**3aj**, **3ak**, **3al** and **3am**). Unfortunately, primary and aryl amines were not suitable for this reaction (**3an** and **3ao**). It is likely that primary amines were oxidized to imines under the reaction conditions.[18] Puzzlingly, 1-methylpiperazine gave only the C-H amination product, and the C-C bond cleavage product was not observed.

Subsequently, the substrate scope of amides was explored (Figure 2). For 8-aminoquinolinebenzamides, a series of halogens on the phenyl ring (**1b**-**1e**) were compatible with the present reaction, and desired products **3aa** were isolated from50% to 74% yields. Other substrates with electron-withdrawing or electron-donating group, such as **1f**, **1g**, **1h**, **1i**, **1j** and **1k** were also subjected to this system, and the corresponding products were isolated in moderate yields. In

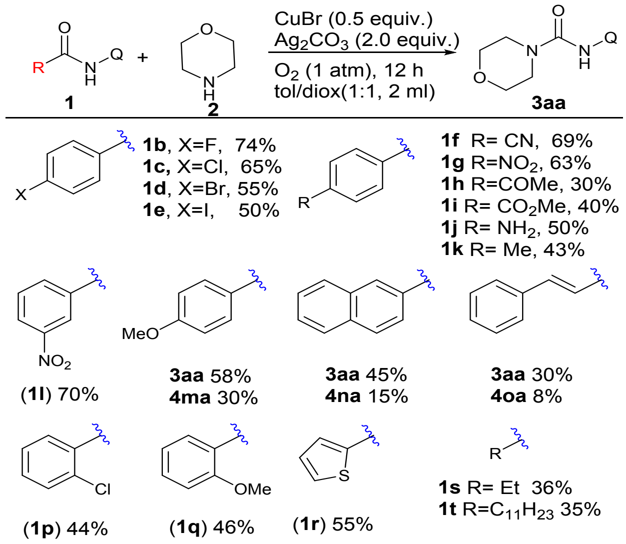
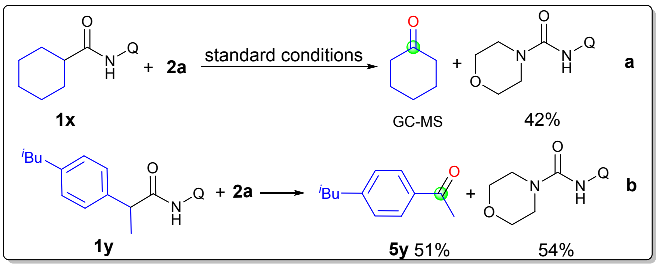


Figure 2 The scope of amides

addition, **1l** could be smoothly transformed to the desired product in 70% yield. Interestingly, **1m** provided the C-C bond cleavage and C-H amination products in 58% (**3aa**) and 30% (**4ma**) yields, respectively, under the standard conditions. Similar phenomena occurred with **1n**, **1o** as reactants. Substrates with ortho groups on the benzene such as **1p** and **1q** gave the expected products in 44% and 46% yields. Heterocyclic benzamides such as **1r** was tolerated in this transformation. Alkyl amides such as (**1s**) and (**1t**) successfully underwent this transformation, with lower yields than aryl amides, this might be because the 2^{o} carbon radical with an electron-withdrawing group is less stable than allyl radical.

To identify part products delivered by amides cleavage, the reaction of **1x** and **2a** was analysed by GC-MS, and cyclohexanone was found (Scheme 3, **a**). Furthermore, when **1y** was used as a substrate, the **5y** was isolated in 51% yield along with 54% **3aa** (Scheme 3, **b**).



Scheme 3 Ketone formation

To elucidate the reaction mechanism, several control experiments were conducted (Please see SI). First, N-(naphthalen-1-yl)benzamide or N-phenylbenzamide instead of 1a were treated with morpholine under the standard conditions, and no desired product was observed, indicating that the directing group is necessary (SI, scheme 1, **a**). Next, when the substrate was switched to N-methylated **1a**, the reaction was virtually stopped, which indicated that a nitrogen-copper complex was generated in the reaction (**b**).

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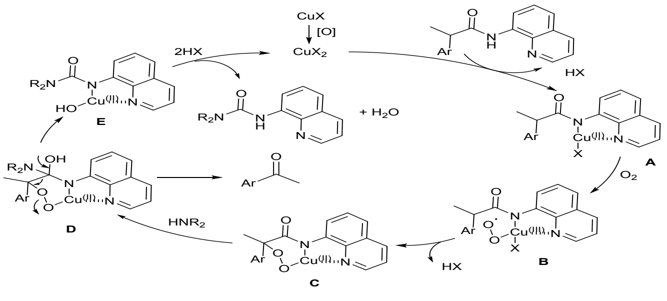
Subsequently, the reaction of O^{18} labelled **1a** was carried out, the desired product was isolated in 68% yield, showed that the reaction did not involve decarbonylation (**c**). 2,3,4,5,6-Pentafluoro-N-(quinolin-8-yl)benzamide and 2,6-dimethyl-N-(quinolin-8-yl)benzamide were tested as substrates, and the desired urea was obtained in 25% and 32% yields, respectively, suggesting that a C-M bond was not produced from C-H bond of the amide and the metal catalyst in this reaction (**d**). When 2,3,4,5,6-pentamethylbenzoic acid derivative was subjected to the reaction, poor result was obtained, but phenol was detected by GC-MS, which implies that phenols are produced when the phenyl part of the amide is cleaved (**e**). We think that these phenols were further oxidized under harsh conditions. Radical scavengers such as TEMPO and 1,1-diphenylethylene were added to the standard reactions, the product yield was dramatically decreased, implying that this reaction proceed via a radical mechanism. NBS and AIBN instead of copper were treated in the model reactions, no desired product was found. EtOH instead of amines was employed into the reaction, and no carbamate formed, indicating the reaction did not undergo an amidyl radical, which then via structure resonance to form isocyanate intermediates (**g, h**).

Although the mechanistic details of this reaction are currently unclear, on the basis of the control experiments and previous literature[12b, 13, 14, 19, 20], a plausible mechanism is illustrated (Scheme 4 and SI). First, copper coordinates with the amide to form intermediate **A**. In dioxygen, copper(II) is oxidized to peroxycopper(III) species **B**. Subsequently, an intramolecular radical relay and oxidation of **B** afford **C**. Then, the amine attacks the acyl group to give **D**. An intramolecular rearrangement takes place to generate a ketone and **E**. With acid assistance, the corresponding urea is generated, and the formed copper(II) continues the catalytic cycle.



Scheme 4 . Reaction mechanism

Conclusions

In conclusion, we have demonstrated the copper-catalyzed direct C-C bond cleavage of amides with 8-aminoquinoline as a directing group. The studies described here showed that the catalyst and dioxygen played important roles in the selectivity of the reaction. The scope of this transformation is broad. A possible mechanism of this reaction was proposed based on several detailed experiments.

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Conflicts of interest

There are conflicts to declare.

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