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# Copper(i)-catalyzed radical carboamination reaction of 8-aminoquinoline-oriented buteneamides with chloroform: synthesis of $\beta$ -lactams†

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A novel Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub>-catalyzed carboamination reaction of 8-aminoquinoline-oriented buteneamides with chloroform to afford 4-(2,2,2-trichloroethyl)- $\beta$ -lactams is described. The reaction proceeded at 110 °C in air with di-*t*-butyl peroxide. Preliminary studies indicated that the reaction undergoes a free radical mechanism *via* a Cu(I)/Cu(II)/Cu(III) catalytic cycle.

## Introduction

Nitrogen-containing heterocycles are notable compounds known for their bioactivity in nature.<sup>1</sup> In particular, functionalized  $\beta$ -lactams are the core skeleton of many natural products and antibiotics drug molecules with specific effects, such as penicillins,<sup>2</sup> carbapenems,<sup>3</sup> cephalosporins<sup>4</sup> and monocyclic  $\beta$ -lactams<sup>5</sup> (Fig. 1).

These  $\beta$ -lactams are known for their clinical use as antibiotics, which have high medicinal synthetic value due to their low toxicity, good bactericidal activity and wide indications.<sup>6</sup> Therefore, during the past 2 decades, great efforts have been focused on the core skeleton construction of  $\beta$ -lactams in synthetic chemistry, such as the Staudinger ketene-imine [2 + 2] cycloaddition,<sup>7</sup> Beckmann rearrangement,<sup>8</sup> Kinugasa alkyne-nitrene cycloaddition,<sup>9</sup> and Schmidt reactions,<sup>10</sup> Until now, the C(sp<sup>3</sup>)-H bond activation,<sup>11</sup> C-C,<sup>12</sup> C-N,<sup>13</sup> C-P,<sup>14</sup> and C-S<sup>15</sup> bond strategy have provided a straightforward pathway to synthesize  $\beta$ -lactams.

The research groups of Shi firstly used transition metal palladium-catalyzed intramolecular amination of aliphatic or amino acid derivatives with different guiding groups to generate  $\alpha$ -amino- $\beta$ -lactam.<sup>16</sup> Afterwards, Wu group has also demonstrated that the propionamide-linked bidentate aminoquinoline (AQ or Q) directing group can facilitate the C(sp<sup>3</sup>)-H activation under Pd catalysis.<sup>17</sup> The research groups of Ge,<sup>18</sup> Kanai<sup>19</sup> and Chantani<sup>20</sup> used transition metal like nickel, cobalt and copper catalyst to generate  $\alpha$ -amino- $\beta$ -lactam by

intramolecular amination of aliphatic or amino acid derivatives with different guiding groups (Scheme 1a). The C-H functionalization strategy is more efficient and convenient than classic intramolecular condensation and nucleophilic reactions. However, the difficulty of these methods was that it first need to obtain functionalized acids as the reaction substrates through monoarylation.

Later, on the basis of the reaction of nucleophiles and 8-aminoquinoline-oriented buteneamide compounds in the Engle's research group,<sup>21</sup> our group first used buteneamide compounds as substrates to oxidize toluene with DTBP to generate benzyl radicals, then benzyl radicals attacked inactive double bonds, and coordinated with copper to generate  $\beta$ -lactams successfully.<sup>22</sup> The reaction mode is efficient and can enrich the preparation method of  $\beta$ -lactam. Subsequently, Chen<sup>23</sup> group used *cis*-3-hexenamide compounds with 8-amino-5-iodoquinoline as the substrates, 4-benzyl Hantzsch esters as the alkyl radical precursor, and rarely used biaryl diphosphine oxide as a chiral ligand to synthesize a series of chiral  $\beta$ -lactam compounds (Scheme 1b). In order to verify the applicability of this method, we tried other free radicals. Doyle<sup>24</sup> and Sheng<sup>25</sup> used chloroform as a solvent and a source of free radicals to achieve the functionalization of unsaturated double bond. It

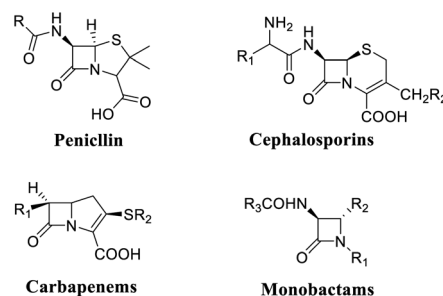


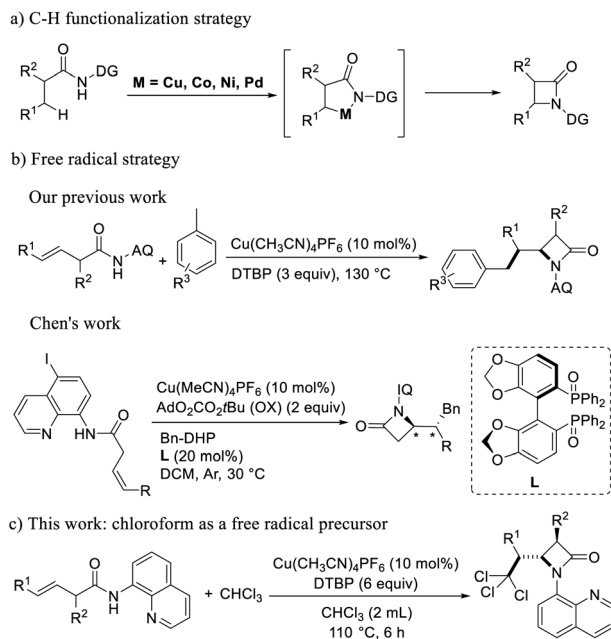
Fig. 1 Natural products and antibiotics drug molecules.

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Scheme 1 One step intramolecular amination reaction.

can be seen that chloroform is a good source of polychloromethyl radicals.<sup>26</sup> Therefore, we used chloroform as the free radical source and found that the chloroform was decomposed into trichloromethyl radicals triggered by DTBP, and then reacted with 8-aminoquinoline-oriented buteneamide compounds to achieve the 2,2,2-trichloroethyl- $\beta$ -lactams (Scheme 1c).

## Results and discussion

When the model reaction of the directing group-protected butenoic acid derivative (**1a**) with chloroform was performed in the presence of oxidants such as *tert*-butyl hydroperoxide (TBHP), no desired products were obtained (Table 1, entries 7). After the addition of 10 mol% di-*t*-butyl peroxide (DTBP), the reaction proceeded smoothly to afford the desired product, 2,2,2-trichloroethyl- $\beta$ -lactam (**2a**).

From the experiment results we can see that trichloromethyl free radical in the presence of copper(i) and DTBP carry out the cascade radical addition/intramolecular amination to perform 2,2,2-trichloroethyl- $\beta$ -lactam in a single step. When the crotonamide compound **1a** with 8-aminoquinoline guiding group was reacted with copper acetate (10 mol%) and DTBP (5 equiv.) in chloroform at 110 °C for 6 h, the cyclized product **2a** was obtained in 45% yield, and some of the starting material was recovered (Table 1, entry 2). Encouraged by this result, several Cu catalysts such as most commonly used CuBr, CuBr<sub>2</sub>, Cu(OTf)<sub>2</sub>, Cu(acac)<sub>2</sub> and Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub> were tested and the results showed that both Cu(i) and Cu(ii) salt could get product **2a**. Interestingly, Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub> gave the best yield of **2a** at 88% (Table 1, entry 6).

The control experiment also clearly showed that Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub> and di-*tert*-butyl peroxide were indispensable for this reaction. Additionally, increasing the amount of DTBP to 6

Table 1 Optimization of reaction conditions<sup>a</sup>

Entry	Catalyst (%)	Oxidant	Temperature	Base	Yield <sup>b</sup>
1	CuBr	DTBP	110 °C		50%
2	Cu(OAc) <sub>2</sub>	DTBP	110 °C		45%
3	Cu(OTf) <sub>2</sub>	DTBP	110 °C		76%
4	CuBr <sub>2</sub>	DTBP	110 °C		62%
5	Cu(acac) <sub>2</sub>	DTBP	110 °C		61%
6	Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub>	DTBP	110 °C		88%
7	Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub>	TBHP	110 °C		0%
8	Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub>	DTBP	110 °C		92%
9	Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub>	DTBP	120 °C		41%
10	Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub>	DTBP	100 °C		83%
11	Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub>	DTBP	90 °C		tr
12	Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub>	DTBP	110 °C	Na <sub>2</sub> CO <sub>3</sub>	44%
13	Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub>	DTBP	110 °C	K <sub>2</sub> HPO <sub>4</sub>	53%

<sup>a</sup> Reaction condition: **1a** (0.2 mmol), DTBP (1 mmol), Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub>, (0.02 mmol), chloroform (2 ml), at 110 °C in air atmosphere, 6 h.  
<sup>b</sup> Yields are given for isolated products. <sup>c</sup> DTBP (1.2 mmol).

equiv. gave a higher yield of **2a** at 92% yield (Table 1, entry 8). However, as the reaction temperature rises to 120 °C, the yield of product **2a** was reduced to 41% (Table 1, entry 9). The reaction could hardly go on when temperature was below 90 °C (Table 1, entry 11). To further improve the efficiency of the free radical reaction, we added several base to reaction system, but this measure has no effect (Table 1, entry 12-13).

With the optimized reaction conditions established, we examined the substrate scope of *N*-(quinolin-8-yl)but-3-enamide derivatives under optimized conditions: DTBP as an oxidant, Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub> as a catalyst at 110 °C, for 6 hours in air. As can be seen from the Table 2, the most  $\alpha$ -substituted *N*-(quinolin-8-yl)but-3-enamide derivatives were well tolerated. Mono-substituted *N*-(quinolin-8-yl)but-3-enamide derivatives were all compatible and had less effect on the C-H activation reaction. Various functional groups, like methyl, ethyl, methylcyclopropyl and benzyl *etc.*, gave the corresponding products (**2b–2m**) in moderate to good yields. Unfortunately, when there were two methyl groups at  $\alpha$  position, the  $\beta$ -lactam product yield was only 43% (**2n**). When the  $\gamma$ -substituted *N*-(quinolin-8-yl)but-3-enamide derivatives were used as the substrates, the products were obtained in low yields (**2o–2q**), and a large amount of raw materials were not reacted completely. It may abate the activity of the reaction substrates due to steric hindrance.

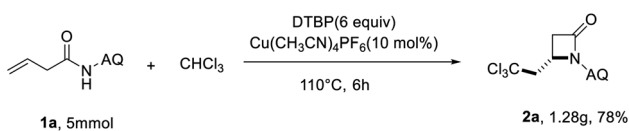
To further demonstrate the synthetic utility of the reaction, the gram-scale reaction was further performed. We found that the corresponding  $\beta$ -lactam product **2a** was acquired in 78% yield under the optimized reaction conditions (Scheme 2).

In order to understand the carboamination reaction mechanism better, we did the following control experiments (Scheme 3).



Table 2 Scope studies of 2,2,2-trichloroethyl- $\beta$ -lactams<sup>a</sup>

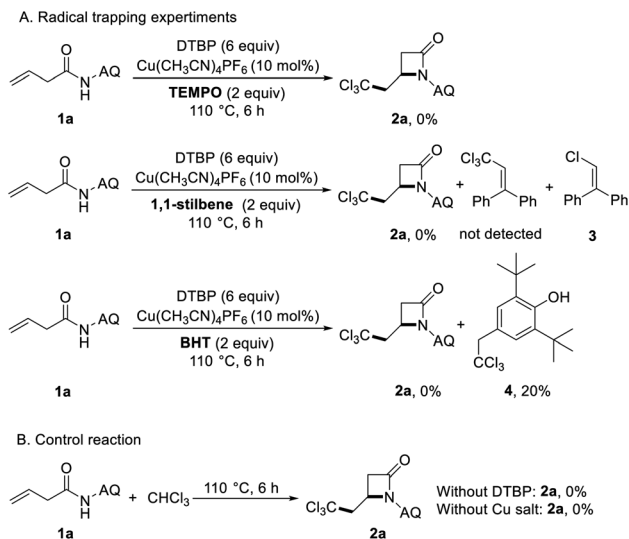
<sup>a</sup> Reaction condition: **1a** (0.2 mmol), DTBP (1.2 mmol), Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub> (0.02 mmol), chloroform (2 ml), at 110 °C in air atmosphere, 6 h. Yield of isolated products are given. 'dr' decided by NMR is >20 : 1 if not stated otherwise.



Scheme 2 Gram-scale reaction.

First, we carried out the radical inhibition and capture experiment. When 2 equiv. of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) was added in the reaction system under standard conditions, the target product was not produced. It showed that the reaction may be a way of free radical reaction.

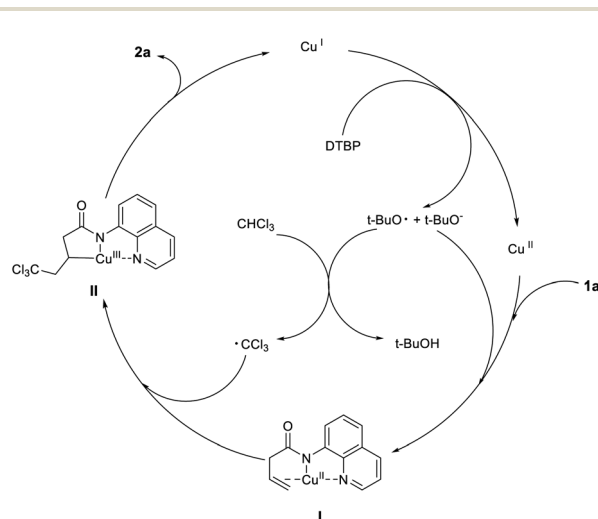
When using 1,1-stilbene to capture free radicals, we didn't detect the presence of trichloromethyl radical capture product, but obtained chlorine radical capture product **3**. This may be due to the decomposition of trichloromethyl radicals into chlorine radicals and dichloromethyl carbene. Since Ghosh



Scheme 3 Control experiments.

research group captured the tribromomethyl radical by using 2,6-di-*tert*-butyl-4-methylphenol (BHT) successfully,<sup>27</sup> we try to capture the trichloromethyl radical by using the same method. It's exciting to obtain the BHT trapped trichloromethyl radical compound **4** (Scheme 3A). And then, when copper salt and DTBP were not added to the reaction system, the reaction did not proceed, which showed that copper salt and DTBP are very important in the reaction (Scheme 3B).

On the basis of the mechanistic studies and experimental results, a plausible mechanism is proposed in Scheme 4. Initially, the copper(I) catalyst reacted with di-*tert*-butyl peroxide, leading to the copper(II) catalyst, *tert*-butoxy radical and *tert*-butoxy anion. Thereafter, *tert*-butoxy radical reacted with chloroform to generate trichloromethyl radicals and *tert*-butoxy anion pulled out the hydrogen on the nitrogen of the reaction substrate (**1a**), the copper(II) catalyst was coordinated with nitrogen anion to form intermediate I. Finally, the



Scheme 4 Proposed reaction mechanism.



intermediate I captured the trichloromethyl radical to form the intermediate II,<sup>28</sup> which was reduced and eliminated to obtain the target product **2a** and copper(I) catalyst. Preliminary studies indicated that the reaction undergoes a free radical mechanism via a Cu(I)/Cu(II)/Cu(III) catalytic cycle.

## Conclusions

In conclusion, a novel method for carbon–nitrogen bond formation was developed through the carboamination reaction of 8-aminoquinoline-oriented buteneamides with chloroform catalyzed by 10% Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub>. The reaction proceeded at 110 °C in air with di-*t*-butyl peroxide to afford 4-(2,2,2-trichloroethyl)-β-lactams from medium to good yields. Further we will find new free radicals and expand the applicability of the free radical reaction to form β-lactams.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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