ORGANIC CHEMISTRY FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2025, **12**, 856

TBN-promoted regioselective C–C bond cleavage: a new strategy for the synthesis of unsymmetrically substituted *N*-aryl oxalamides†

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Received 22nd October 2024,
Accepted 28th November 2024

DOI: 10.1039/d4qo01984a

rsc.li/frontiers-organic

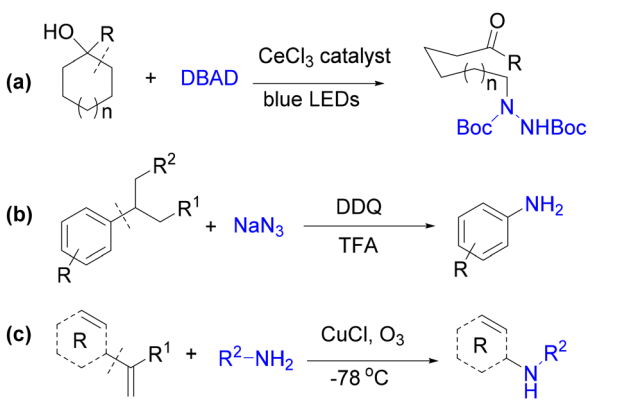
Intermolecular regioselective C–C and C–O bond cleavage and amination were accomplished using a $CuCl_2$–TBN system under mild reaction conditions. This protocol represents a simple, efficient and highly functional group compatible method for the synthesis of unsymmetrically substituted *N*-aryl oxalamides. The present reaction opens an alternative path using H_2O as the source of oxygen for the preparation of *N*-aryl oxalamides *via* regioselective C–C and C–O bond cleavage and the formation of two new C–N bonds.

Introduction

C–C bonds are prevalent in organic compounds, and direct C–C functionalization has attracted great interest from chemists because the strategy provides a direct chemical transformation to reorganize complex carbon skeletons.[1,2] However, C–C bond activation remains a technical challenge due to the high bond energy (average 90 kcal mol^{-1}) and the difficulty of selective cleavage in molecules with multiple C–C bonds.[3]

Recently, very important advances have sought to address the challenge of C–C σ bond activation.[4] In this case, transition-metal-catalyzed C–C σ bond activation and transformation with alkynes, alkenes, carbenoids, imines, CO and other substrates have been successively developed.[5–11] However, the activation of C–C σ bonds and their conversion to C–N bonds has been rarely reported. For example, the Zuo group employed $CeCl_3$/visible-light-induced amination of cycloalkanols with di-*tert*-butyl azodicarboxylate (DBAD) to achieve C–C σ bond cleavage and transformation (Scheme 1a).[12] The Jiao group revealed a significant breakthrough by demonstrating unstrained linear C–C bond cleavage and amination of alkylarenes for the construction of new C–N bonds with sodium azides utilizing DDQ as an oxidant (Scheme 1b).[13] The Kwon group employed ozonolysis and copper catalysis to enable alkene C–C σ bond cleavage for new C–N bond formation (Scheme 1c).[14] Despite these advances, C–C σ bond activation and amination are basically limited to construct C(sp^3)–N bonds. In comparison, the direct amination of unstrained arylketone Csp^2–Csp^2 σ bonds to construct C–N bonds remains challenging. Because of their higher thermodynamic stability likely due to the π–π conjugation effect and the uncertainty of the N-source substitution during the amination process, selective C–C bond cleavage becomes difficult. Recently, the Zeng group reported Rh(III)-catalyzed activation of unstrained arylketone Csp^2–Csp^2 σ bonds to construct C–N bonds (Scheme 3a).[15] Although the transformations are attractive, they are associated with rare metal catalysts; the nitrogen source is also limited to azides. In view of the difficulty in using noble metal catalysts for C–C bond cleavage and amination, we need to develop inexpensive metal catalysts and mild reaction conditions for C–N bond construction.

Among many C–N compounds, *N*-aryl oxalamides are widely used in blood clotting, ambenonium (a cholinesterase inhibitor), IDO-1 inhibitors, antimalarial agents, and entry



Scheme 1 Unstrained sp^3 C–C bond activation to the C–N bond.

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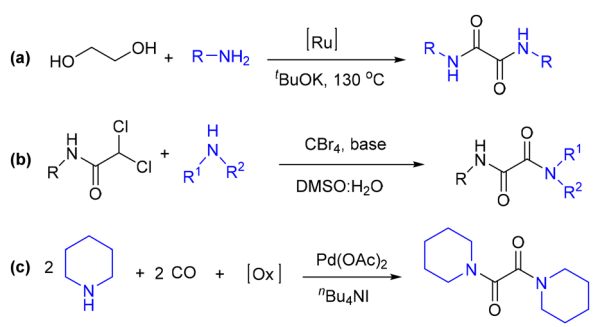
† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d4qo01984a

inhibitors that target the CD_4-binding site of HIV-1.[16,17] They are also utilized as flavoring agents in food processing and have been identified as effective ligands for combining with Cu complexes for the formation of potent catalytic systems that facilitate coupling reactions involving C–O/C–N bond formation.[18] Thus, the development of new and effective methods for the preparation of oxalamides is of utmost importance and has garnered significant attention in the field. Traditional synthetic strategies for *N*-aryl oxalamides require expensive metal catalysts or harsh reaction substrates (Scheme 2).[19] As a result, the pursuit of atom-economical and environmentally friendly techniques for the efficient synthesis of oxalamides is considered crucial and a priority for the chemical and pharmaceutical sectors. We were interested in Cu-catalyzed C–C bond cleavage and amination for their structural diversity, commercial availability, and nontoxicity.[20] Therefore, we envisage to use cheap metal catalysts, oxygen sources, and widely available C–C bond compounds to achieve the synthesis of *N*-aryl oxalamides by C–C bond cleavage. To confirm our hypothesis, we need to select compounds that contain a variety of C–C bonds to realize regioselective C–C bond cleavage and amination for the production *N*-aryl oxalamides.

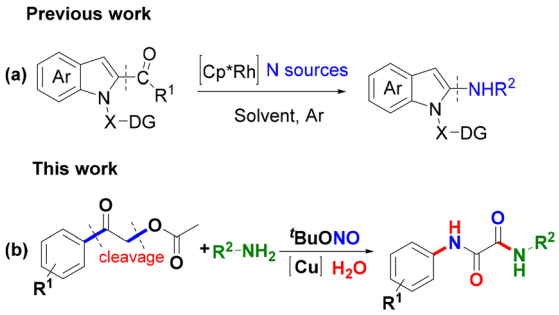
Substituted 2-oxo-2-phenylethyl acetate compounds were synthesized *via* a simple step and used as substrates, [Cu] was used as the catalyst, and green H_2O and TBN were used as the source of oxygen. To our delight, the desired *N*-aryl oxalamide products were obtained (Scheme 3b). This strategy features the following: the cheaper [Cu] as the catalyst and TBN as the oxidant; TBN and H_2O as the oxygen source; regioselective C–C and C–O bond cleavage; double C–N bond formation in one pot; and a novel approach for the synthesis of diverse unsymmetrical oxalamide derivatives.

Results and discussion

To identify the suitable reaction conditions for the synthesis of oxalamides from substituted 2-oxo-2-phenylethyl acetate and primary amines, initial optimization studies were performed with 2-oxo-2-phenylethyl acetate **1a** and *n*-propylamine **2a** as the model substrates in the presence of *tert*-butyl nitrite (TBN) and H_2O, and the results are summarized in Table 1. Gratifyingly, N^1-phenyl-N^2-propyloxalamide **3a** was obtained in

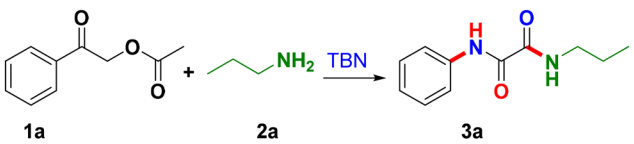


Scheme 2 The route towards the synthesis of *N*-aryl oxalamides.



Scheme 3 Unstrained sp^2 C–C bond activation to the C–N bond.

Table 1 Optimization of the model reaction conditions[a]



1a **2a** **3a**

Entry	Catalyst	Solvent	**3a**[b]
1	CuI	C_2H_5OH	35%
2	$Cu(CH_3COO)_2$	C_2H_5OH	65%
3	Cu_2O	C_2H_5OH	47%
4	$Cu(CO_2CH_3)_2{\cdot}H_2O$	C_2H_5OH	45%
5	$CuSO_4$	C_2H_5OH	54%
6	$CuCl_2{\cdot}2H_2O$	C_2H_5OH	60%
7	**$CuCl_2$**	**C_2H_5OH**	**78%**
8	$CuCl_2$	1,4-Dioxane	Trace
9	$CuCl_2$	Chlorobenzene	Trace
10	$CuCl_2$	DCE	Trace
11	$CuCl_2$	Acetonitrile	40%
12	$CuCl_2$	DMF	55%
13	$CuCl_2$	Dimethylsulfoxide	60%
14	$CuCl_2$	Isopropanol	63%
15	$CuCl_2$	Methanol	70%
16	$FeCl_3$	C_2H_5OH	—
17	$Ni(CH_3COO)_2{\cdot}4H_2O$	C_2H_5OH	30%
18	$CuCl_2$ (30%)	C_2H_5OH	30%
19	$CuCl_2$ (50%)	C_2H_5OH	18%
20	$CuCl_2$ (100%)	C_2H_5OH	—
21	—	C_2H_5OH	—
22[c]	$CuCl_2$	C_2H_5OH	58%
23[d]	$CuCl_2$	C_2H_5OH	72%
24[e]	$CuCl_2$	C_2H_5OH	65%
25[f]	$CuCl_2$	C_2H_5OH	70%

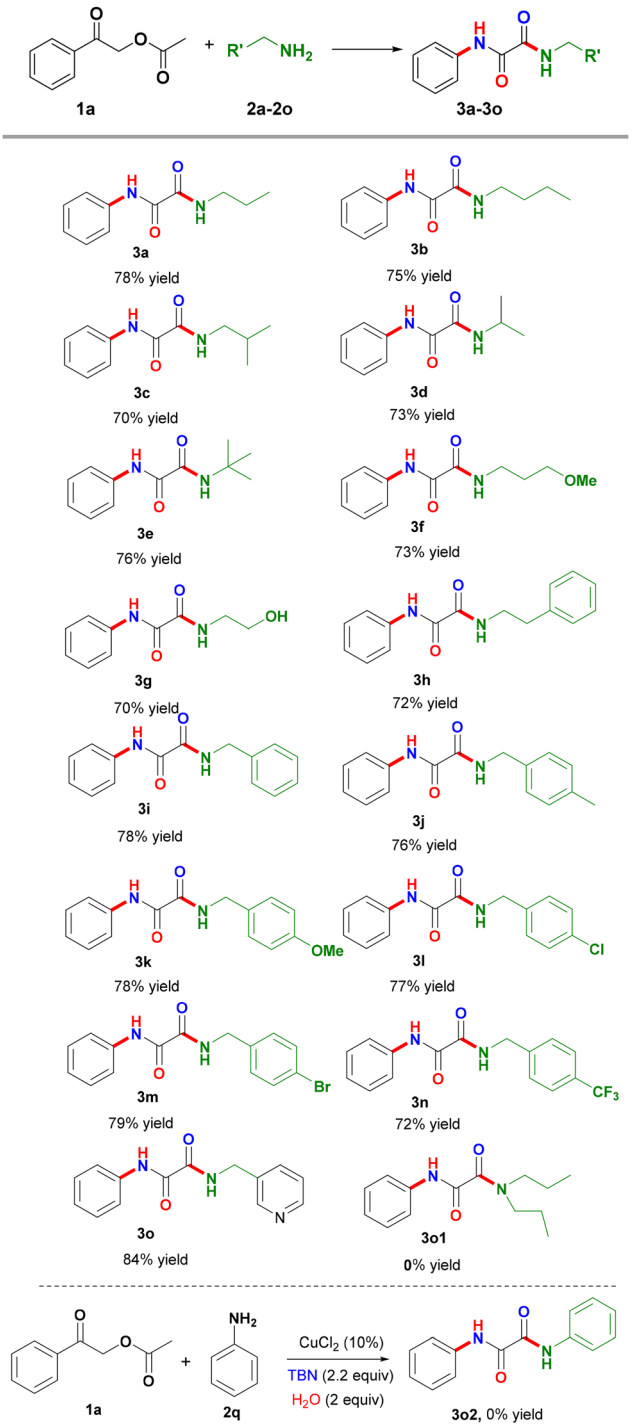
[a] Reaction conditions: 2-oxo-2-phenylethyl acetate **1a** (0.2 mmol), *n*-propylamine **2a** (0.26 mmol), TBN (0.44 mmol), catalyst (0.02 mmol), solvent (2 mL, H_2O 0.2 mmol), N_2 in a 25 mL Schlenk tube, 120 °C, 12 h. [b] Isolated yield. [c] TBN (0.6 mmol). [d] TBN (0.4 mmol). [e] 100 °C. [f] 140 °C.

35% yield (Table 1, entry 1). We next conducted a survey of several catalysts (Table 1, entries 2–7); to our delight, the yield of **3a** could be slightly increased to 78% using $CuCl_2$ as the catalyst (Table 1, entry 7). Solvent screening showed that most of the tested solvents including 1,4-dioxane, chlorobenzene, DCE, acetonitrile, DMF, dimethylsulfoxide, isopropanol and methanol could not increase the yield of this transformation (Table 1, entries 8–15). We investigated the catalyst scope of the reaction, including Fe and Ni, and the desired product **3a**

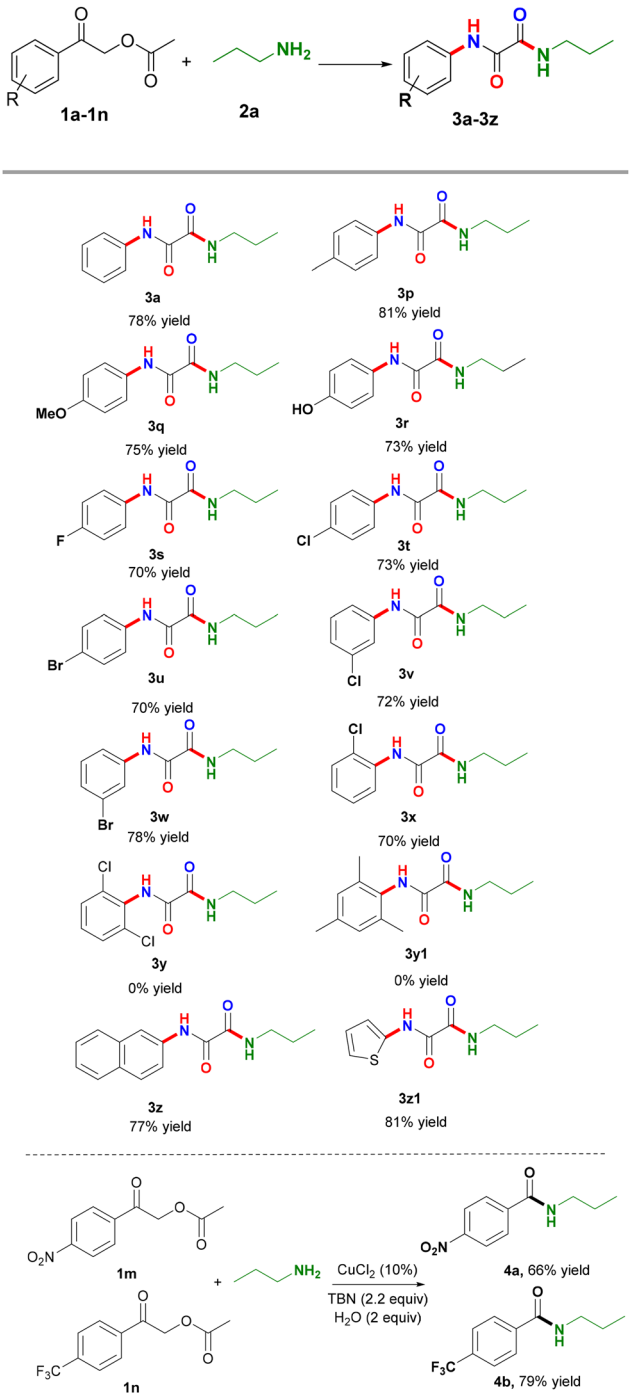
was not detected when using $FeCl_3$ as the catalyst (Table 1, entry 16). With 10% $Ni(CH_3COO)_2{\cdot}4H_2O$ as the catalyst, the reaction proceeded to form product **3a** in 30% yield (Table 1, entry 17). The loading of $CuCl_2$ catalysts was screened, and the results showed that with the increase of catalytic loading, the yield of the desired product **3a** gradually decreased and even disappeared (Table 1, entries 18–20). Compound **3a** was not obtained in the absence of the catalyst $CuCl_2$, which demonstrated that the catalyst $CuCl_2$ played a key role in this transformation (Table 1, entry 21). We then switched our attention to changing the amount of TBN, and it turned out that when 3.0 equiv. of TBN were used, the yield of **3a** decreased significantly and the by-products increased, while when 2.0 equiv. of TBN were used, the yield of **3a** decreased and the raw material **1a** did not react completely (Table 1, entries 22 and 23). The effect of temperature on product formation was also studied subsequently. It was observed that the yield of **3a** decreased when the reaction temperature was reduced to 100 °C or increased to 140 °C (Table 1, entries 24 and 25). Thus, the optimized conditions for the synthesis of **3a** can be defined as follows: 2-oxo-2-phenylethyl acetate **1a** (0.2 mmol), *n*-propylamine **2a** (0.26 mmol), TBN (0.44 mmol) and $CuCl_2$, at 120 °C for 12 h.

Having established the optimal conditions for this tandem reaction (Table 1, entry 7), the substrate scope of a wide variety of primary amines and substituted 2-oxo-2-phenylethyl acetate compounds was explored (Schemes 4 and 5). Under the optimized conditions, a wide range of aliphatic primary amines **2a–2q** were competent in this reaction, indicating that the reaction is generally applicable to produce unsymmetrically substituted *N*-aryl oxalamides *via* C–C and C–O bond cleavage and amination, as summarized in Scheme 4. Firstly, we found that primary amines, secondary amines and tertiary amines **2a–2e** could readily react with 2-oxo-2-phenylethyl acetate to give the corresponding oxalamides in 76–78% yields (**3a–3e**). Then, the substitution effect on the aliphatic amine chain was examined. The results disclosed that both electron-donating (–OMe, –Ph) and electron-withdrawing (–OH) groups were suitable and afforded the corresponding oxalamide products in moderate to good yields (**3f–3h**). Moreover, diverse substituted benzylamines were tested in this reaction, and the results showed that the substrates bearing different substituents on the phenyl ring including –Me, –OMe, halogens (–Cl, –Br), and $-CF_3$ were well tolerated and resulted in the target products in 72–79% yields (**3i–3n**). Heteroaryl benzylamine **2o** was also compatible and converted to the corresponding oxalamide **3o** in 84% yield. Disappointingly, secondary amines were not tolerated to give the desired product **3o1** under the present reaction conditions, and the phenomenon can be explained by the following mechanism: only primary amines are compatible due to the large steric hindrance during the addition process. Aromatic amines were not tolerated to produce the desired product **3o2**, which may be attributed to the weak electrophilicity of aromatic amines due to the strong conjugation effect between the electrons of the N atom and the benzene ring.

The scope of substituted 2-oxo-2-phenylethyl acetate compounds was examined with *n*-propylamine under the optimized reaction conditions, as summarized in Scheme 5. A wide range of substituted 2-oxo-2-phenylethyl acetate compounds were tolerated in this reaction. For the synthesis of substituted *N*-aryl oxalamides, variation of the substituent group in terms of position and electronic character noticeably



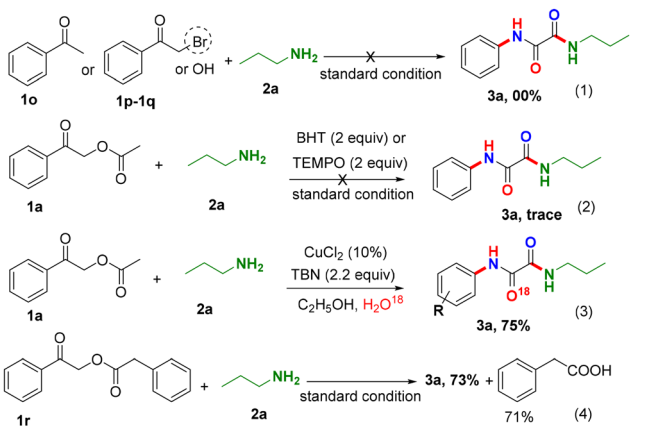
Scheme 4 Scope of amine substrates. Reaction conditions: 2-oxo-2-phenylethyl acetate **1a** (0.2 mmol), amines **2a–2q** (0.26 mmol), TBN (0.44 mmol), $CuCl_2$ (0.02 mmol), C_2H_5OH (2 mL, H_2O 0.2 mmol), N_2 in a 25 mL Schlenk tube, 120 °C, 12 h, isolated yield.



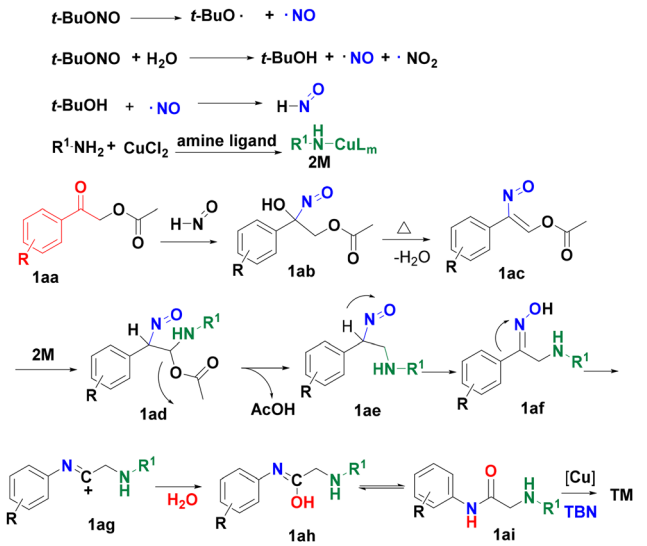
Scheme 5 Scope of substituted 2-oxo-2-phenylethyl acetate compounds. Reaction conditions: substituted 2-oxo-2-phenylethyl acetate **1a–1p** (0.2 mmol), *n*-propylamine **2a** (0.26 mmol), TBN (0.44 mmol), $CuCl_2$ (0.02 mmol), C_2H_5OH (2 mL, H_2O 0.2 mmol), N_2 in a 25 mL Schlenk tube, 120 °C, 12 h, isolated yield.

affected the reaction efficiency. Notably, the aromatic ring bearing *para*-substituted groups including –Me, –OMe, –OH and halogens (–F, –Cl, –Br) did not have an obvious steric hindrance effect, and resulted in the target products in 70–81% yields. Moreover, 2-oxo-2-phenylethyl acetate compounds with *ortho*- and *meta*-substituted groups (–Br, Cl) were also suitable substrates under standard reaction conditions to give the corresponding oxalamides **3v–3x** in 70–72% yields. In another respect, when 2-(2,6-dichlorophenyl)-2-oxoethyl acetate and 2-mesityl-2-oxoethyl acetate were used as substrates, the corresponding oxalamides **3y** and **3y1** were not detected, which is ascribed to the large steric hindrance and strong electronic effect at the *ortho* position limiting the rearrangement reaction. Interestingly, the reaction of the naphthalene-containing substrate **2l** proceeded smoothly to form *N*-aryl oxalamide **3z** in a yield of 77%. Heteroaryl 2-oxo-2-phenylethyl acetate also afforded the *N*-aryl oxalamide **3z1** in 81% yield *via* regioselective C–C and C–O bond cleavage. However, when 2-oxo-2-phenylethyl acetate compounds substituted with strong electron-withdrawing groups $-CF_3$ and $-NO_2$ were used as substrates, the corresponding oxalamides were not produced under standard reaction conditions, while amides **4a** and **4b** were obtained *via* Csp^2–Csp^3 bond cleavage. In general, the Beckmann rearrangement is affected by the electronic effect, and the substrates with electron-withdrawing groups showed poor reaction efficiency.

To illustrate a probable reaction pathway for this one-pot synthesis of unsymmetrically substituted *N*-aryl oxalamides, some control experiments were carried out, as shown in Scheme 6. When acetophenone **1o**, 2-bromoacetophenone **1p**, or 2-hydroxy-1-phenylethan-1-one **1q** replaced 2-oxo-2-phenylethyl acetate as the substrate, the corresponding oxalamide **3a** was not detected (Scheme 6(1)), suggesting that this is not an interim process in the present reaction system. When the radical scavenger 2,2,6,6-tetramethylpiperidinyloxy (TEMPO, 2 equiv.) or butylated hydroxytoluene (BHT, 2 equiv.) was added to the reaction mixture, the desired product **3a** was obtained in 15% or 18% yield (Scheme 6(2)), respectively, which suggested that a radical pathway is probably involved in the procedure. To obtain the source of the oxygen atoms, since the reaction did not proceed under oxygen conditions, we added H_2O^{18} to the reaction system under otherwise identical conditions (all raw materials and solvents were treated *via* standard anhydrous procedures), and the ^{18}O labelled product **[^{18}O]-3a** was generated in 75% yield (Scheme 6(3)), as deter-



Scheme 6 Control experiments.



Scheme 7 Plausible reaction pathway for the synthesis of unsymmetrically substituted *N*-aryl oxalamides.

mined by LC-MS (see the ESI†). Incorporation of the ^{18}O-labeled product suggested that the oxygen from water is the possible source of oxygen in the *N*-aryl oxalamide product and the other oxygen originates from TBN. To confirm the by-products during the reaction process, 2-oxo-2-phenylethyl 2-phenylacetate **1r** was used as the substrate; **3a** was obtained in 73% yield (Scheme 6(4)) and phenylacetic acid was detected in 71% yield, proving that C–O bond cleavage is really involved in the present reaction system.

According to the reported literature[20,21] and the control experiments above, the possible TBN-promoted regioselective C–C and C–O bond cleavage pathway for the synthesis of substituted *N*-aryl oxalamides is proposed as shown in Scheme 7. The copper catalyst with the amine forms the iminium-type intermediate **2M**.[20] *t*-BuONO easily decomposes to generate the *t*-butyloxy radical and nitric oxide radical, or *tert*-butyl nitrite reacts with water to afford the desired free radicals of NO and NO_2.[21a] The reaction of NO radicals with *t*-Bu-OH forms the active HNO species, and the addition of HNO to CO in **1aa** yields **1ab**.[21b] Compound **1ac** is formed through thermal dehydration, and the addition of **2M** to **1ac** forms **1ad**.[21c] This process is affected by steric hindrance and subsequent release of AcOH as a leaving group leads to the formation of **1ae**,[21e] which transforms into intermediate **1ai** *via* a Beckmann rearrangement.[21d] The substituted *N*-aryl oxalamide **TM** is obtained through oxidation of the C–H bond using TBN as an oxidant and $CuCl_2$ as a catalyst.[21f]

Conclusions

In summary, we report a novel strategy *via* $CuCl_2$–TBN-mediated regioselective C–C and C–O bond cleavage for the construction of new C–N bonds. The protocol provides an efficient approach for the synthesis of unsymmetrically substituted *N*-aryl oxalamides in moderate to good yields under mild reaction conditions. The reaction has a satisfactory substrate scope and functional group compatibility, and features good reaction efficiency to provide a novel route towards the synthesis of *N*-aryl oxalamides *via* regioselective C–C and C–O bond cleavage.

Data availability

All data supporting the results of this study are available within the article and its ESI.† Source data are provided with this paper.

Conflicts of interest

We declare that we have no competing financial interests.

Acknowledgements

We thank Dr Long Liu of Hainan University for the assistance with the plausible reaction pathway, discussions and advice. Financial support was provided by the National Natural Science Foundation of China (22378102) and the special fund for the Key Laboratory of Hubei Province (2022ZX04).

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