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Copper-catalyzed amidoalkylation of amines *via* C–C bond cleavage from cyclic oxaziridines

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Here, we report a copper-catalyzed C–C bond cleavage of cyclic oxaziridines and a C(sp³)–N coupling reaction with amines. The reaction, which proceeds under mild conditions and features simple operation and an ideal 100% atom economy, enables the synthesis of a wide variety of functionalized amides in moderate to excellent yields. Density functional theory (DFT) calculations reveal

that copper initially catalyses N–O bond cleavage to generate an N-radical species, which in turn induces β -scission of the C–C bond by producing an amidoalkyl radical species. This reactive amidoalkyl radical species is subsequently trapped by amine nucleophiles, furnishing the final products after a C(sp³)–N reductive elimination process.

Green foundation

1. We report an efficient copper-catalyzed protocol for the C–C bond cleavage of cyclic oxaziridines and the subsequent C(sp³)–N coupling with amines, which proceeds under mild, redox-neutral conditions with 100% atom economy.
2. The reaction demonstrates excellent functional group compatibility, allowing smooth amidoalkylation of structurally diverse nitrogen nucleophiles to afford the corresponding 6-amino hexanamides in moderate to excellent yields. Additionally, it enables ring-opening/amination transformations for both strained and unstrained cyclic systems.
3. In future work, we intend to explore efficient coupling reactions between various nucleophiles and cyclic oxaziridines with 100% atom economy.

Introduction

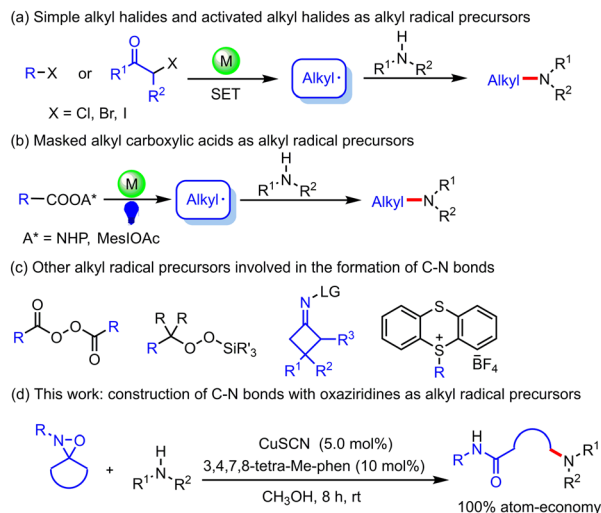
Nitrogen-containing compounds are common structural motifs in natural products, pharmaceuticals, agrochemicals and functional materials such as amino acids, nucleic acids, and alkaloids and play a crucial role in chemistry and biology.¹ Consequently, establishing a powerful synthetic platform for the rapid construction of C–N bonds has been the subject of significant research efforts in academia as well as in industry. Classical transition-metal-catalyzed reactions, including Ullmann aminations, Chan–Lam aminations, and Buchwald–Hartwig reactions, have been well developed and widely applied to the construction of C(sp²)–N bonds.² To form

C(sp³)–N bonds, reliable ionic-pathway-based procedures including nucleophilic substitution (S_N1 or S_N2) reactions, reductive amination with carbonyls, hydroamination or diamination of alkenes, transition-metal-catalyzed amination of alkyl electrophiles and other reactions have all been successfully developed.³ However, these transformations have faced some challenging issues, including overalkylation, poor efficiency with bulky substrates, β -hydride elimination and the difficulty in C(sp³)–N reductive elimination. In recent years, free radical chemistry has presented a highly advantageous approach for achieving transition-metal-catalyzed amination of alkyl electrophiles.⁴ For example, simple and activated alkyl halides can be reduced by copper complexes *via* single-electron transfer (SET) processes to generate alkyl radicals, which would undergo C(sp³)–N cross-coupling (Scheme 1a).⁵

Additionally, Hu, MacMillan and others have made significant progress in decarboxylative amination of masked alkyl carboxylic acids such as alkyl NHPI esters and iodomesitylene dicarboxylates using synergetic photoredox/copper-catalytic reaction systems (Scheme 1b).⁶ Diacyl peroxides,⁷ alkylsilyl peroxides,⁸ cyclobutanone oxime esters,⁹ alkylthianthrenium

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Scheme 1 Transition-metal-catalyzed amination of alkyl electrophiles.

salts¹⁰ and other compounds were subsequently proven to serve as efficient sources of alkyl radicals. Under thermal conditions, transition-metal catalysis or irradiation, they can generate the corresponding alkyl radicals, which would then undergo the $C(sp^3)-N$ cross-coupling reaction (Scheme 1c). Despite these remarkable developments, most of the above precursors have functional groups that need to be removed during the process of generating the alkyl radical. It is still highly desirable to develop more efficient precursors to provide alkyl radicals and achieve the direct construction of $C(sp^3)-N$ bonds with 100% atom economy.

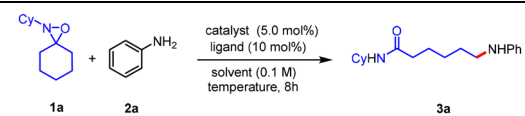
Oxaziridines, by virtue of their weak N–O bond and strained three-membered heterocyclic ring, display abnormal stability and distinctive reactivities, and have been used as powerful and elegant oxygen- and nitrogen-transfer agents for a broad array of nucleophiles.¹¹ Asymmetric transformations including oxidation and amination have also seen significant progress.^{11,12} Moreover, oxaziridines could undergo various intramolecular radical rearrangements, isomerization and cyclization under transition-metal catalysis or photochemical conditions.^{11,13} During these transformations, carbon radicals have been shown to be generated from nitrogen radicals *via* the selective cleavage of C–C bonds.^{13a,14} Based on this concept, the Maruoka group independently developed efficient protocols for generating alkyl radicals from oxaziridines, which were trapped by various 1,1-diarylethylenes to yield Heck-type products.¹⁵ Moreover, these alkyl radicals could also successfully participate in copper-catalyzed decarboxylative $C(sp^2)-C(sp^3)$ coupling of α,β -unsaturated carboxylic acids.¹⁶ However, to the best of our knowledge, only these two types of radical acceptors have been successfully applied to capture the alkyl radicals, so it remains both necessary and highly desirable to investigate more efficient nucleophiles for such transformations and broaden the frontier of oxaziridine chemistry.

Our group has a strong interest in radical-mediated carbon–carbon bond cleavage and subsequent functional-

ization transformations. A wide range of nitrogen nucleophiles has been employed to trap the alkyl radicals generated from iminyl-radical-initiated carbon–carbon bond cleavage, providing a useful approach for $C(sp^3)-N$ bond formation.^{9a} Based on this discovery and previous reports, we set out to pursue the challenging $C(sp^3)-N$ bond coupling of cyclic oxaziridines with amines, aiming at incorporating the important alkyl-substituted amide moieties into structurally diverse nitrogen-containing molecules, especially bioactive natural products and drugs, with 100% atom economy (Scheme 1d).

Our investigation began with an examination of the reaction between oxaziridine **1a** and aniline **2a** in the presence of copper(i) catalysts and 1,10-phen at 60 °C for 8 h. To our delight, the reaction occurred and gave the desired *N*-cyclohexyl-6-(phenylamino)hexanamide **3a** in 25% yield with 100% atom economy (Table 1, entry 1). Other solvents, including EtOH, toluene and acetonitrile were less effective for this reaction (entries 2–4). The effect of different nitrogen ligands including dtbpy, terpy, 5,6-di-Me-phen and 3,4,7,8-*tetra*-Me-phen was then examined, and the choice of 3,4,7,8-*tetra*-Me-phen afforded the highest chemical yield (entries 5–8). Notably, even when the reaction temperature was lowered from 60 °C to room temperature, the reaction continued to proceed smoothly, affording **3a** in a satisfactory yield of 46% (entry 9). Screening of copper catalysts revealed CuSCN to be the most effective catalyst (entries 10–13), whereas other catalysts such as PdCl₂ and CoBr₂ were found to be inert for this transformation (entry 14). To our delight, the yield of **3a** was improved from 58% to 79% when the ratio of **1a** to **2a** was optimized at

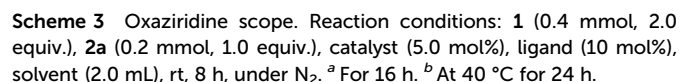
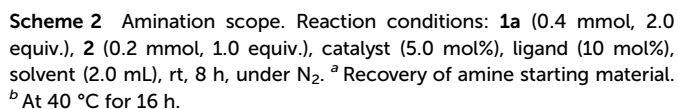
Table 1 Optimization of reaction conditions^{a,b}

					
Entry	Catalyst	Ligand	Solvent	Temp. (°C)	Yield (%)
1	CuI	1,10-phen	CH ₃ OH	60	25
2	CuI	1,10-phen	EtOH	60	11
3	CuI	1,10-phen	Toluene	60	0
4	CuI	1,10-phen	CH ₃ CN	60	0
5	CuI	dtbpy	CH ₃ OH	60	15
6	CuI	terpy	CH ₃ OH	60	20
7	CuI	5,6-Di-Me-phen	CH ₃ OH	60	38
8	CuI	3,4,7,8- <i>tetra</i> -Me-phen	CH ₃ OH	60	45
9	CuI	3,4,7,8- <i>tetra</i> -Me-phen	CH ₃ OH	rt	46
10	CuBr	3,4,7,8- <i>tetra</i> -Me-phen	CH ₃ OH	rt	30
11	CuBr ₂	3,4,7,8- <i>tetra</i> -Me-phen	CH ₃ OH	rt	23
12	Cu(OTf) ₂	3,4,7,8- <i>tetra</i> -Me-phen	CH ₃ OH	rt	15
13	CuSCN	3,4,7,8- <i>tetra</i> -Me-phen	CH ₃ OH	rt	58
14	PdCl ₂ or CoBr ₂	3,4,7,8- <i>tetra</i> -Me-phen	CH ₃ OH	rt	0
15 ^c	CuSCN	3,4,7,8- <i>tetra</i> -Me-phen	CH ₃ OH	rt	79
16 ^c	None	3,4,7,8- <i>tetra</i> -Me-phen	CH ₃ OH	rt	0
17 ^c	CuSCN	None	CH ₃ OH	rt	0

^a Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.4 mmol, 2.0 equiv.), catalyst (5.0 mol%), ligand (10 mol%), solvent (2.0 mL), rt, 8 h, under N₂. ^b Isolated yield. ^c **1a** (0.4 mmol, 2.0 equiv.), **2a** (0.2 mmol, 1.0 equiv.).

With the optimal reaction conditions in hand, we set out to evaluate the generality and limitations of this ring-opening/amination reaction with 2-cyclohexyl-1-oxa-2-azaspiro [2.5] octane **1a** as the model substrate (Scheme 2). The results showed that aryl amines bearing electron-withdrawing groups (Cl, Br, I, CF₃, CN, *etc.*) on the *para*-position of the phenyl ring all reacted smoothly and delivered the desired products **3b–3h** in moderate to high yields. However, the electron-rich aromatic amines **2i** and **2j** were less efficient under the standard reac-

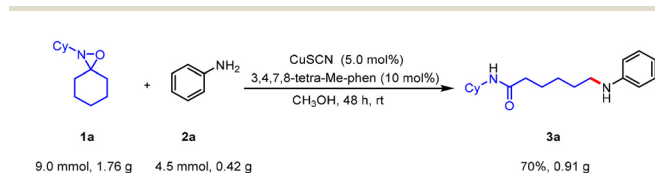
Subsequently, we evaluated the scope of oxaziridines **1** using aniline **2a** as the model nucleophile under this copper-catalytic system (Scheme 3). Satisfactorily, the 4-, 5-, 7-, 8-, and 15-membered cyclic oxaziridines furnished the corresponding amides **4a–4e** in moderate to good yields *via* ring opening of



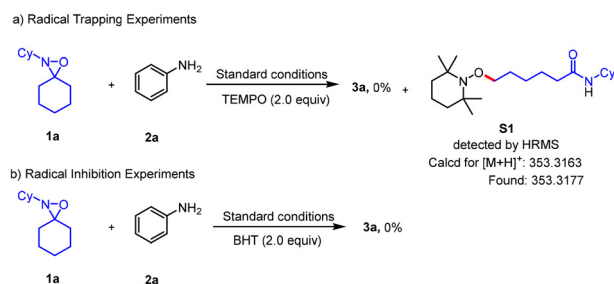
the cycloalkyl moiety of the oxaziridine. Oxaziridine **1f**, bearing an oxygen atom on the cycloalkane ring, was well tolerated in the reaction, affording **4f** in 70% yield. To our delight, oxaziridine **1g** derived from 4-phenylcyclohexanone also furnished the target product, namely **4g**, in a high yield of 72%.

Interestingly, when 2-cyclohexyl-4-methyl-1-oxa-2-azaspiro[2.5]octane **1h** was subjected to the standard conditions, two types of 6-aminohexanamides, **4h** and **4h'**, were detected in a ratio of more than 2 : 1. This phenomenon can be explained by the regioselectivity of the ring-opening amination reaction. The reaction preferentially occurred at the carbon atom adjacent to the methyl substituent, leading to the formation of a relatively stable alkyl radical for the construction of the C–N bond. Benzocyclohexanone-derived oxaziridine could efficiently participate in the C–C bond cleavage, affording the expected product **4i** in 45% yield. Luckily, when the substituent on the nitrogen was changed to a tosyl group, the anticipated product **4j** could still be obtained, albeit in relatively low yield. In contrast, replacing the nitrogen protecting group with *n*-hexyl precluded the formation of ring-opening amination product **4k**. Furthermore, when the acyclic oxaziridine **1l** (derived from methyl isopropyl ketone) was used in the C–C cleavage/amination reaction, isopropylamine **4l** was obtained in a yield of 63%.

The utility of this protocol was illustrated by performing a gram-scale synthesis (Scheme 4). When the reaction of **1a** with **2a** was conducted on a 4.5 mmol scale, **3a** was obtained in 70% yield, showing a yield and selectivity comparable to those for the small-scale reactions.



Scheme 4 Large-scale experiment.



Scheme 5 Mechanism studies.

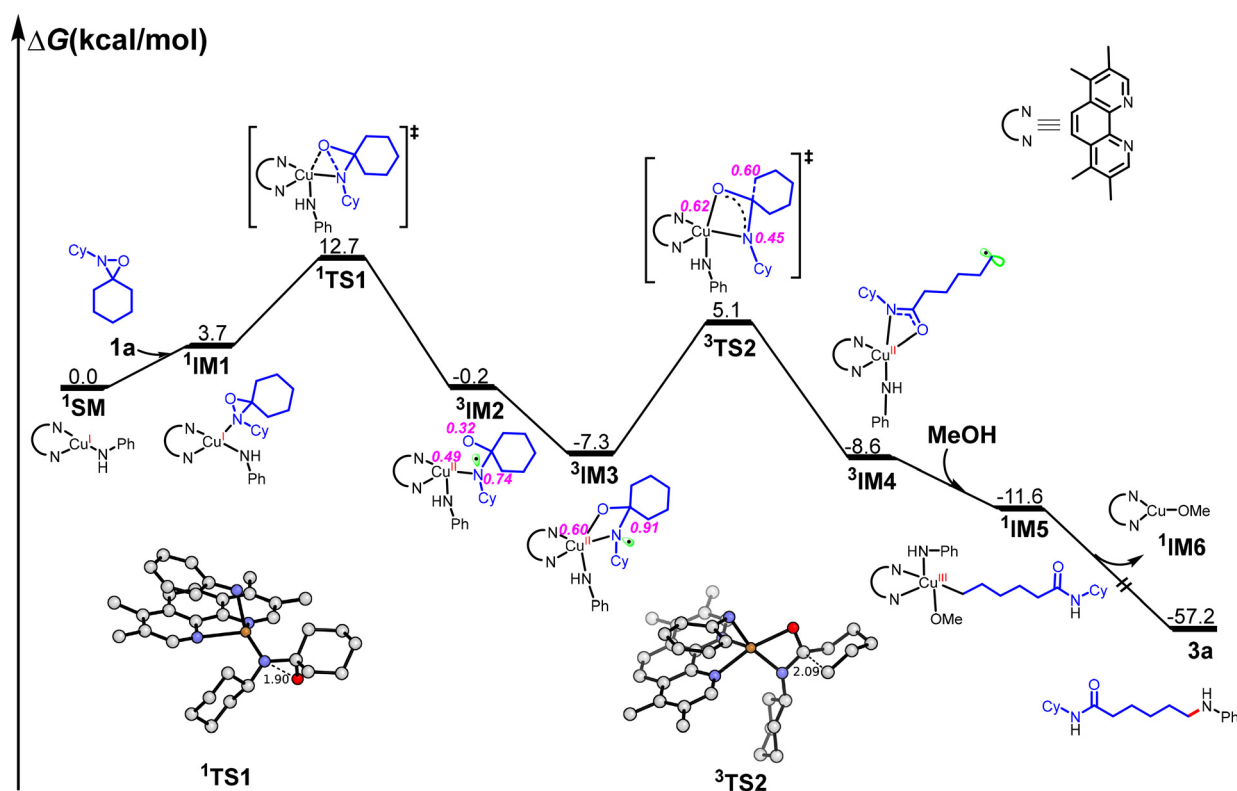


Fig. 1 Computed Gibbs free energy profile of the Cu-catalyzed amidoalkylation of amines. The left superscripts 1 and 3 of each species represent singlet and triplet states, respectively. 3D structures of key transition states are given, but the hydrogens are omitted for clarity. Energies are in kcal mol^{−1}. Spin density values are labelled in magenta. Distances are given in Ångströms (Å).

To shed light on the reaction mechanism, control experiments were carried out (Scheme 5a and b). When 2.0 equiv. of TEMPO or BHT was added under the standard reaction conditions, the reaction was suppressed completely, and the alkyl-TEMPO adduct **S1** was detected using HRMS. These results suggested a probable involvement of an alkyl radical intermediate in this transformation.

Density functional theory (DFT) calculations were performed to learn more about the reaction mechanism, and the resulting Gibbs free energy profile for the reaction is shown in Fig. 1. Initially, according to the proposed mechanism, oxaziridine **1a** coordinates to active catalyst **¹SM**, producing the Cu(I) species **¹IM1** (3.7 kcal mol⁻¹), with this process consistent with previous calculations by Maruoka.¹⁵ **¹IM1** then undergoes N–O bond cleavage *via* the transition state **¹TS1** at the closed shell with an energy barrier of 12.7 kcal mol⁻¹, affording the d⁹-centered Cu(II) species **³IM2**; this cleavage is the rate-determining step. **³IM2** is understood to result from homolysis of the N–O bond, accompanied by electron transfers from Cu to the O atom. Subsequently, penta-coordinated copper complex **³IM3** (–7.3 kcal mol⁻¹) is formed with a release of 7.1 kcal mol⁻¹ of energy. The spin density analysis carried out on O, N and Cu atoms further indicated the N-radical species **³IM3** to be more stable than the O-radical species **³IM2**. Finally, the N-radical species **³IM3** induces β-scission *via* **³TS2** with an energy barrier of 12.4 kcal mol⁻¹. Compared to the values for **³IM3**, the spin density on N of **³TS2** is decreased by 0.46 and that on C is simultaneously increased to 0.60, affording the amidoalkyl radical intermediate **³IM4** with –8.6 kcal mol⁻¹ energy. The d⁸-metal-centered Cu(III) species **¹IM5** (–11.6 kcal mol⁻¹) is formed by a thermodynamically favorable transmetalation between MeOH and **³IM4**, and a classical reductive elimination of **¹IM5** is exothermic, specifically with a change in energy of –45.6 kcal mol⁻¹, leading to the final product **3a**.

Conclusions

In summary, we have successfully established an efficient copper-catalyzed ring opening of cyclic oxaziridines under mild and redox-neutral conditions, affording amidoalkyl radicals through a sequential cleavage of the N–O and C–C bonds. Structurally diverse nitrogen nucleophiles, including (hetero) aromatic amines, aromatic N-heterocycles, alkyl amines, and amides, were utilized to trap these amidoalkyl radicals, thus providing an efficient and green synthetic route to structurally diverse 6-aminohexanamides in moderate to excellent yields with 100% atom economy. Moreover, the reaction could be performed on a gram scale, demonstrating its applicability in synthetic chemistry.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the SI.

The optimization process of experimental conditions, specific procedures for the reaction, relevant characterization data of products, and data from the calculation section are all included in the Supplementary Information files. See DOI: <https://doi.org/10.1039/d5gc03001c>

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