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Letter

# Copper-Catalyzed Enantioconvergent Radical C(sp$^3$)−N Cross-Coupling to Access Chiral α-Amino-β-lactams

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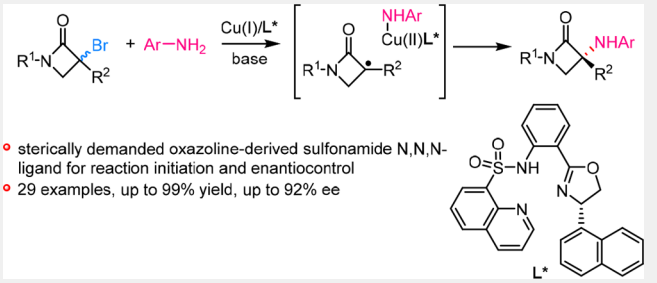
**ABSTRACT:** A copper-catalyzed enantioconvergent radical C(sp$^3$)−N cross-coupling of racemic tertiary α-bromo-β-lactams with aromatic amines is developed under mild thermal reaction conditions. The use of a sterically demanded oxazoline-derived sulfonamide N,N,N-ligand is crucial for the reaction initiation and effective enantio-discrimination of the azetidinone-derived cyclic alkyl radicals. The strategy provides an attractive approach to access chiral α-amino-β-lactams, an important structural motif in many biologically active molecules. Preliminary mechanistic studies support the formation of azetidinone-derived alkyl radicals from the **L***Cu(I)-amido complex and α-bromo-β-lactams.




**KEYWORDS:** *copper, asymmetric radical reactions, cross-coupling, aromatic amines, chiral α-amino-β-lactams*



Chiral β-lactams, an important class of heterocyclic compounds, are present in a wide range of natural products and pharmaceutical molecules.[1−3] Among them, chiral α-amino-β-lactams with pronounced biological activities have attracted the interest of synthetic organic chemists.[4−7] Notable examples of these chiral α-amino-β-lactams have attractive antibacterial activities, such as penicilliums,[5] nocardicins,[6] and sulfazecin[7] (Scheme 1A). As a result, a variety of synthetic strategies have been elegantly developed for the construction of chiral α-amino-β-lactams.[4,8−11] Among them, the most popular strategy is the asymmetric Staudinger [2 + 2] cycloaddition,[8] which has been successfully applied to the synthesis of antibiotic precursors containing chiral α-amino-β-lactams, such as loracarbef[12] and Gram-negative strains[13] (Scheme 1B, left). However, traditional approaches generally rely on the utilization of chiral auxiliaries. Recently, catalytic asymmetric versions of the reaction have also been sporadically reported.[9] The Mitsunobu-mediated cyclization involving the multistep transformation of a chiral serine-type amino acid provides alternative access to chiral α-amino-β-lactams (Scheme 1B, left).[10] Given the importance of the structural motifs, the development of more catalytic asymmetric methods for the preparation of chiral α-amino-β-lactams remains highly desirable.

In the search for general strategies for the synthesis of chiral α-amino-β-lactams, we turned our attention to the enantioconvergent C(sp$^3$)−N cross-coupling of racemic tertiary α-bromo-β-lactams (Scheme 1B, right). The coupling with tertiary α-bromo-β-lactams offers significant advantages due to their efficient synthesis from readily available starting materials[14] and their ability to introduce various functional groups with precision.[15] Pioneering work by Fu has elegantly demonstrated a nickel-catalyzed enantioconvergent radical C(sp$^3$)−C(sp$^3$) cross-coupling of tertiary α-bromo-β-lactams with alkenes (Scheme 1C).[16] Meanwhile, we have developed copper-catalyzed enantioconvergent radical C(sp$^3$)−C(sp/sp$^2$) cross-coupling of similar alkyl bromides with alkynes and organoboronate esters (Scheme 1C).[17] Despite these significant advances, the enantioconvergent C(sp$^3$)−N cross-coupling of tertiary α-bromo-β-lactams with amines has not yet been reported.

As part of our continuous interest in designing multidentate chiral anionic ligands for copper-catalyzed enantioconvergent radical cross-coupling reactions,[18] we have recently reported a series of copper-catalyzed enantioconvergent C(sp$^3$)−N cross-coupling of acyclic tertiary alkyl halides with amines.[19,20] The crucial step in the coupling with aromatic amines is the utilization of a copper/multidentate N,N,N-ligand catalyst to forge the desired C(sp$^3$)−N bond via the interaction of the acyclic tertiary alkyl radical with **L***Cu(II)-amido complex.[19c] As such, we envisioned that the employment of tertiary α-bromo-β-lactams would extend the scope of cross-coupling chemistry to access chiral α-amino-β-lactams. However, two challenges must be overcome to ensure the success of this reaction. First, can the Cu(I) catalyst reduce alkyl halides to alkyl radicals under mild thermal reaction conditions? Second,

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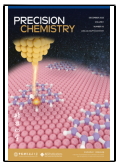





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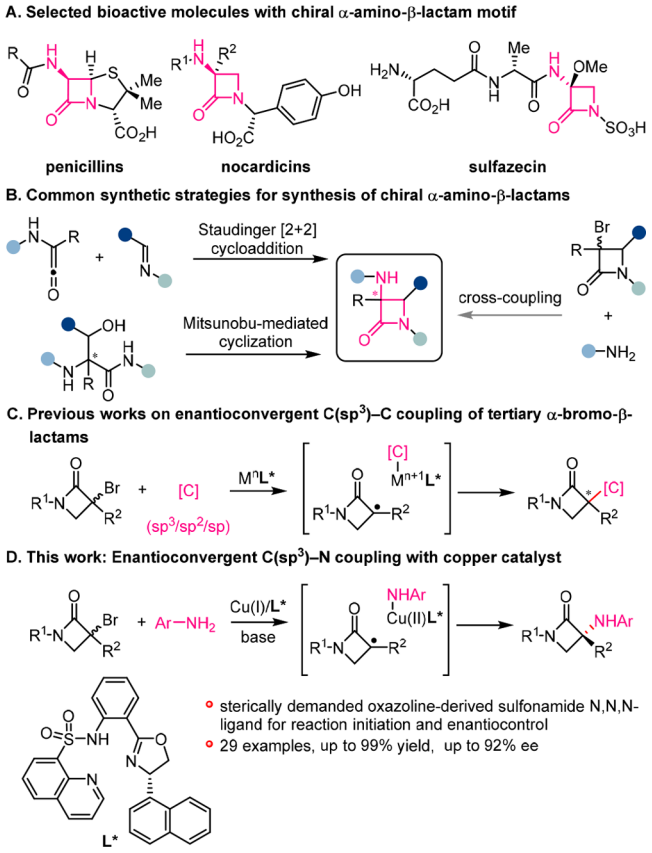
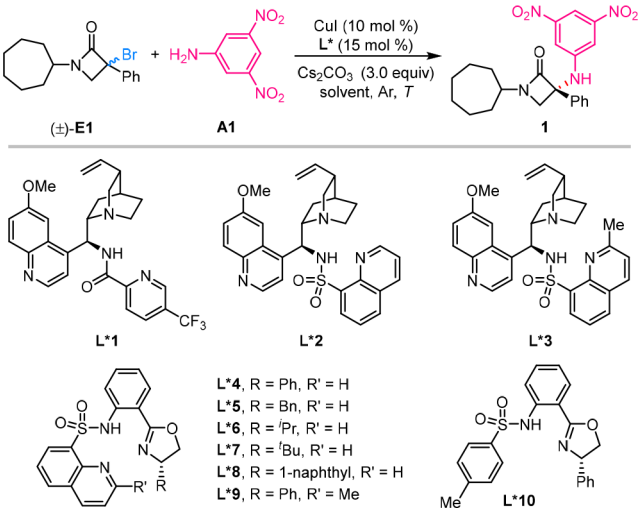
**Scheme 1. Enantioconvergent C($sp^3$)–N Cross-Coupling to Access Chiral $\alpha$-Amino-$\beta$-lactams**




the azetidinone-derived cyclic tertiary alkyl radical possesses relatively small bulkiness compared with the acyclic tertiary alkyl radical, and its enantiocontrol has not been elegantly established. Herein, we report a copper-catalyzed enantioconvergent radical C($sp^3$)–N cross-coupling of racemic tertiary $\alpha$-bromo-$\beta$-lactams with aromatic amines, enabling the synthesis of chiral $\alpha$-amino-$\beta$-lactams with good efficiency and enantioselectivity under mild thermal conditions (Scheme 1D). The success of this strategy relies on the rational design of a sterically demanded oxazoline-derived sulfonamide N,N,N-ligand, which could enhance the reducing capability of Cu(I) catalysts for reaction initiation and allow effective enantio-discrimination of the cyclic tertiary alkyl radical.

To test the feasibility of the hypothesis, we set out to investigate the ligand effect on the model reaction of tertiary $\alpha$-bromo-$\beta$-lactam **E1** and aromatic amine **A1** in the presence of CuI and $Cs_2CO_3$ in benzene at 25 °C (Table 1). The cinchona-alkaloid-derived amide N,N,N-ligand **L*1**[17a] used in our previously reported alkynylation of tertiary $\alpha$-bromo-$\beta$-lactam failed to initiate the single-electron reduction of **E1** under ambient conditions and most of **E1** was recovered (Table 1, entry 1). Instead, the use of cinchona-alkaloid-derived sulfonamide N,N,N-ligand **L*2**[19a] was able to initiate this reaction to give the coupling product **1** in 21% yield with 37% ee (Table 1, entry 2). The success of the N,N,N-ligand **L*2** led us to further investigate N,N,N-ligand **L*3** bearing an ortho substituent,[17b] which was used in our previously reported alkenylation/arylation of tertiary $\alpha$-bromo-$\beta$-lactam. The ee of **1** could not be enhanced, indicating that the enantiocontrol of the copper-amido complex might be different

**Table 1. Optimization of Reaction Conditions**[a]




| entry | ligand | solvent | $T$(°C) | yield (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | **L*1** | benzene | 25 | trace | – |
| 2 | **L*2** | benzene | 25 | 21 | 37 |
| 3 | **L*3** | benzene | 25 | 10 | 10 |
| 4 | **L*4** | benzene | 25 | 85 | 86 |
| 5 | **L*5** | benzene | 25 | 69 | 81 |
| 6 | **L*6** | benzene | 25 | 81 | 74 |
| 7 | **L*7** | benzene | 25 | 86 | 81 |
| 8 | **L*8** | benzene | 25 | 83 | 88 |
| 9 | **L*9** | benzene | 25 | 84 | 56 |
| 10 | **L*10** | benzene | 25 | trace | – |
| 11 | **L*8** | 1,4-dioxane | 25 | 84 | 88 |
| 12 | **L*8** | THF | 25 | 81 | 87 |
| 13 | **L*8** | DME | 25 | 81 | 87 |
| 14 | **L*8** | EtOAc | 25 | 89 | 88 |
| **15** | **L*8** | EtOAc | 10 | 86 | 89 |
| 16 | **L*8** | **EtOAc** | **0** | **86** | **92** |
| 17 | **L*8** | EtOAc | −5 | 83 | 92 |

[a]Reaction conditions: (±)-**E1** (0.05 mmol), **A1** (0.05 mmol), CuI (10 mol %), **L*** (15 mol %), and $Cs_2CO_3$ (3.0 equiv) in solvent (1.0 mL) at $T$ for 72 h under argon; yield of **1** was based on $^1$H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as an internal standard; ee value was based on HPLC analysis.

from that of the copper-alkenyl/aryl complex (Table 1, entry 3). We then turned to the oxazoline-derived sulfonamide N,N,N-ligand,[19c] which performed well in our previously reported C–N coupling. Fortunately, the reaction with **L*4** afforded **1** with higher enantioselectivity than those with cinchona-alkaloid-derived N,N,N-ligands **L*2** and **L*3** (Table 1, entry 4). Various oxazoline-derived sulfonamide N,N,N-ligands were then investigated (Table 1, entries 5–9). Ligand **L*8** with a bulkier 1-naphthyl substituent rather than a phenyl group (**L*4**) on the oxazoline ring gave product **1** in 83% yield with 88% ee (Table 1, entry 8). However, the installation of a bulky group on the coordinating quinoline moiety is deleterious to the enantioselectivity (Table 1, entry 9). A control experiment with an oxazoline-derived sulfonamide N,N ligand **L*10** failed to give the coupling product **1** (**E1** was recovered), indicating the pivotal role of the additional coordination site on the reaction initiation (Table 1, entry 10). A subsequent solvent survey led us to identify EtOAc as the optimal choice (Table 1, entries 11–14). Further investigation of copper catalysts and bases showed no


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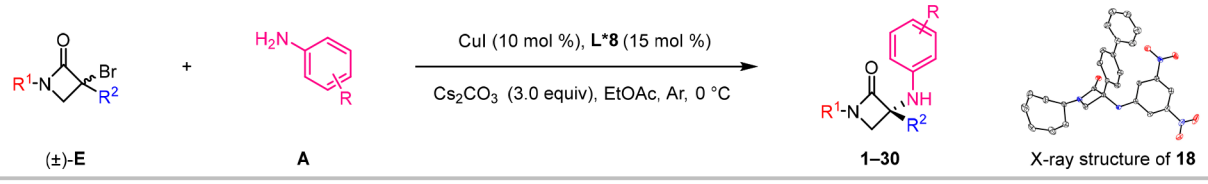
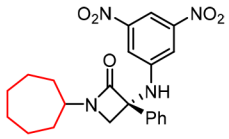
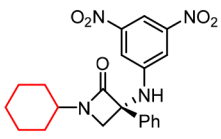
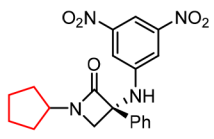
Table 2. Scope of Tertiary $\alpha$-Bromo-$\beta$-lactams and Aromatic Amines[a]

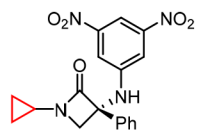


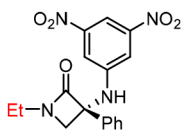

(±)-E A 1–30 X-ray structure of 18

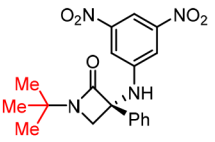

1, 85%, 92% ee

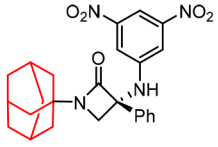

2, 98%, 88% ee

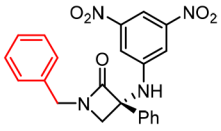

3, 97%, 89% ee

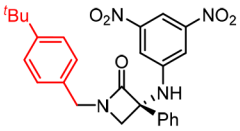

4, 75%, 87% ee

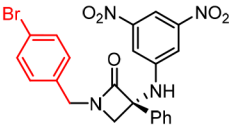

5, 98%, 90% ee

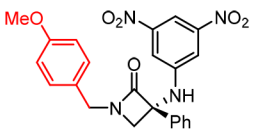

6, 96%, 91% ee

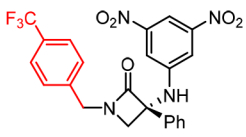

7, 97%, 91% ee

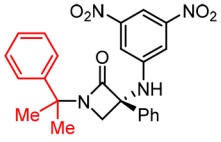

8, 81%, 89% ee

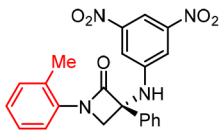

9, 91%, 90% ee

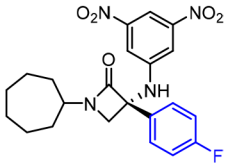

10, 90%, 90% ee

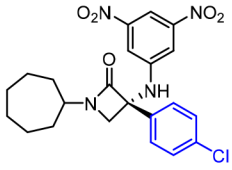

11, 95%, 88% ee

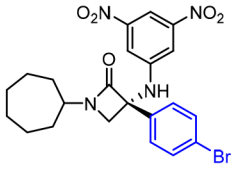

12, 99%, 88% ee

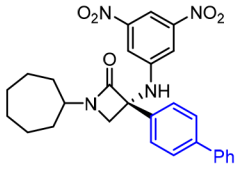

13, 83%, 90% ee

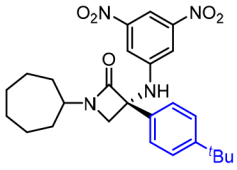

14, 99%, 80% ee

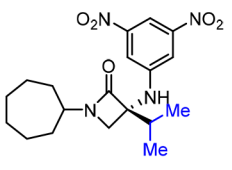

15, 88%, 88% ee

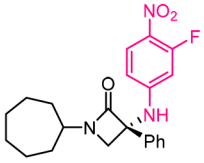

16, 97%, 81% ee

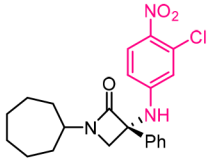

17, 84%, 89% ee

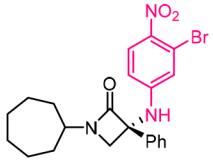

18, 62%, 89% ee

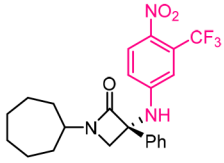

19, 86%, 90% ee

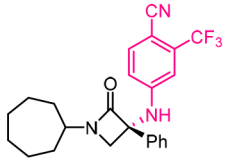

20, 0%

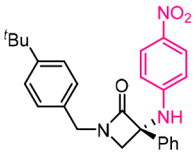

21, 66%, 83% ee

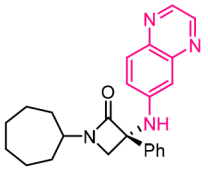

22, 63%, 86% ee

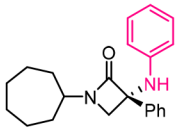

23, 55%, 85% ee

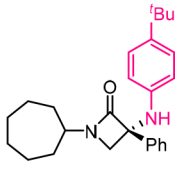

24, 78%, 80% ee

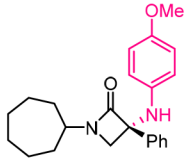

25, 69%, 84% ee


26, 63%, 83% ee


27, 59%, 76% ee


28, 28%, < 5% ee


29, 68%, < 5% ee


30, 56%, < 5% ee

[a]Reaction conditions: (±)-E (0.20 mmol), A (0.20 mmol), CuI (10 mol %), L*8 (15 mol %), and $Cs_2CO_3$ (3.0 equiv) in EtOAc (4.0 mL) at 0 °C for 72 h under argon; yields were isolated ones; ee values were determined by HPLC analysis.

improvement in efficiency and enantioselectivity (Tables S1 and S2 in the Supporting Information). To our delight, lowering the reaction temperature further enhanced the ee without significantly affecting the yield, and the best result was obtained at 0 °C, whereas **1** was obtained in 86% yield with 92% ee (Table 1, entry 16).

Having established the optimal reaction conditions, we investigated the substrate scope for the cross-coupling reaction (Table 2). Concerning the nitrogen of tertiary $\alpha$-bromo-$\beta$-lactams ($R^1$ group in the substrate), many substrates with cyclic ring (**1**–**4**), unfunctionalized aliphatic chain (**5**, **6**), adamantyl ring (**7**), and functionalized benzyl ring (**8**–**13**) were all well accommodated in this process to afford the coupling products in satisfactory yields (75–99%) with 87–92% ee. Furthermore, the aryl substituent (**14**) was also amenable to the reaction. As for the $R^2$ group of tertiary $\alpha$-bromo-$\beta$-lactams, a diverse range of aryl rings were suitable substrates for the reaction to afford **15**–**19** in good yields with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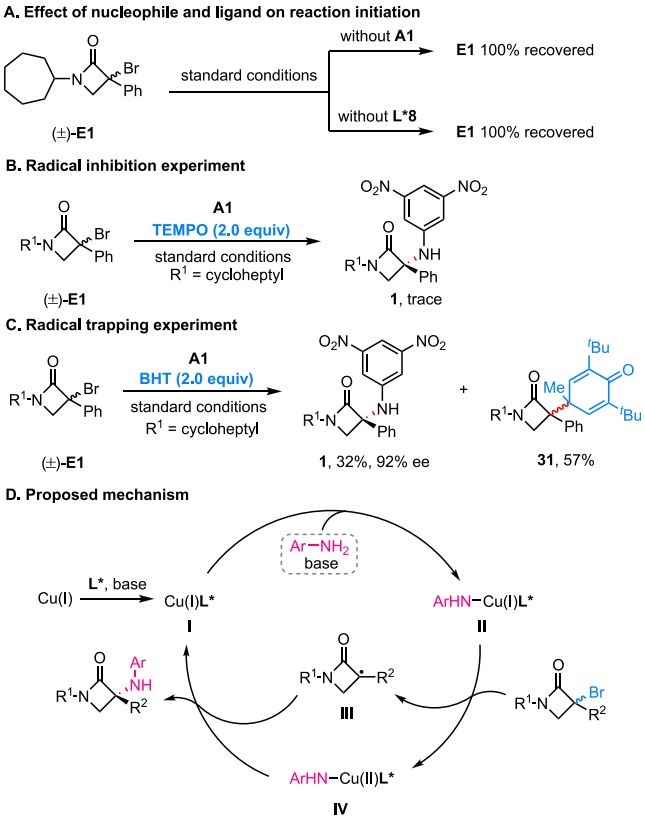
81−90% ee. The reaction tolerated various substituents with different electronic properties on the aryl ring such as halogen (**15**−**17**), Ph (**18**), and $^t$Bu (**19**). However, the alkyl-substituted bromide was not suitable for the reaction. No desired product **20** was obtained and no conversion of alkyl bromide was observed probably because the reducing capability of the Cu(I) catalyst is too weak to reduce **E20** under current reaction conditions. The scope of aromatic amines for this copper-catalyzed cross-coupling reaction was next investigated. In addition to 3,5-dinitroaniline (**A1**), 4-nitroanilines bearing ortho substituents, such as −F (**A2**), −Cl (**A3**), −Br (**A4**) and −$CF_3$ (**A5**), could all be used as effective aromatic amines to afford the corresponding $\alpha$-amino-$\beta$-lactams **21**−**24** in 55−78% yields with 80−86% ee. In addition, other strongly electron-withdrawing (hetero)-aromatic amines, such as 4-amino-2-(trifluoromethyl)-benzonitrile, monosubstituted 4-nitroaniline and quinoxalin-6-amine, could be effectively coupled to furnish the corresponding products **25**−**27** in 59−69% yields with 76−84% ee. Unfortunately, aniline and electron-donating aromatic amines only gave rise to the desired coupling products **28**−**30** with poor ee (<5%). It is probably because the acidity of these anilines is weak and cannot effectively form the Cu-amido complex with copper, as depicted in Scheme 1D. The reactions are currently being further optimized in our laboratory. The absolute configuration of **18** (Table 2 and Figure S1 in the Supporting Information) was determined to be *R* by X-ray crystallographic analysis, and all other compounds were assigned analogously.

In order to gain insight into the reaction mechanism, a series of control experiments were carried out. No conversion of **E1** was observed in the absence of amine **A1** or ligand **L*8** under otherwise identical reaction conditions (Scheme 2A). It indicated that the formation of a chiral ligand-chelated Cu(I)-amido complex (intermediate **II** in Scheme 2D) from **L***, Cu(I), and amine, rather than the single-electron reduction between Cu(I)**L*** and alkyl bromide, is probably the first step in the catalytic cycle. The mechanistic sequence might be probably different from our previously reported C($sp^3$)−C($sp^2$) cross-coupling.[17b] The radical inhibition experiment with 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) showed complete reaction inhibition (Scheme 2B). In addition, the radical trapping experiment with butylated hydroxytoluene (BHT) resulted in a reduced yield of **1** together with the formation of BHT-trapped product **31** under standard conditions (Scheme 2C). Taken together, these results support the involvement of a radical mechanism. Based on the above mechanistic results and our previous studies,[17−19] we proposed a plausible mechanism as shown in Scheme 2D. First, Cu(I) reacted with chiral ligand **L*** to give a Cu(I)**L*** complex **I** in the presence of a base. The subsequent ligand exchange of complex **I** with aromatic amines generated the **L***Cu(I)-amido complex **II**, which reduced tertiary $\alpha$-bromo-$\beta$-lactams via a single electron transfer process to deliver prochiral alkyl radicals **III** and a Cu(II) complex **IV**. Subsequently, the interaction of radical **III** and complex **IV** gave rise to the cross-coupling products and regenerated the catalytic active species **I** for the next cycle. Further experimental studies are underway in our laboratory to delineate the mechanistic details.

In summary, we have developed a copper-catalyzed enantioconvergent radical C($sp^3$)−N cross-coupling of racemic tertiary $\alpha$-bromo-$\beta$-lactams with aromatic amines under mild thermal conditions. The key to the success lies in the use of a

**Scheme 2. Mechanistic Investigation**




sterically demanded oxazoline-derived sulfonamide N,N,N-ligand for both reaction initiation and enantiocontrol over the cyclic alkyl radical intermediate. More importantly, this strategy provides a precise platform for rapid access to valuable enantioenriched $\alpha$-amino-$\beta$-lactams, which are core skeletons of many antibiotic precursors. Further efforts will focus on the development of enantioconvergent radical carbon−heteroatom cross-coupling reactions of tertiary $\alpha$-bromo-$\beta$-lactams with more heteroatomic nucleophiles.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/prechem.3c00084.

Experimental procedures, characterization of compounds (PDF)

Crystallographic data of **18** (CIF)

### Accession Codes

CCDC 2290566 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +441223 336033.

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§J.-J.Z. and W.-L.L. contributed equally. The manuscript was written through the contributions of all authors.

## Notes

The authors declare no competing financial interest.

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