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Copper-Catalyzed Asymmetric Three-Component Radical 1,2-Carboamination of Acrylamides with Arylamines: Access to Chiral α-Tertiary *N*-Arylamines

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Chemistry

The asymmetric radical carboamination of 1.1-disubstituted alkenes from readily available alkyl halides and arylamines provides expedient access to valueadded chiral α -tertiary *N*-arylamines but has been less recognized. A challenge arises mainly from the difficult reaction initiation inherent in alkyl halides and the construction of fully substituted chiral C-N bonds from sterically congested tertiary alkyl radicals. Herein, we report a copper-catalyzed asymmetric three-component radical carboamination of acrylamides utilizing an anionic chiral N.N.N-ligand under mild conditions. This ligand was essential for the reaction initiation by enhancing the reducing capability of copper and enabling the enantiocontrol over tertiary alkyl radicals. The substrate scope was broad, covering an array of acrylamides, aryl- and

heteroaryl-amines, as well as alkyl halides and sulfonyl chlorides, enabling good functional group tolerance. When combined with the follow-up transformation, this strategy provides a versatile platform for accessing structurally diverse chiral α -tertiary *N*-arylamine building blocks of interest in organic synthesis.



Keywords: asymmetric catalysis, copper, alkenes, radical reactions, chiral amines



Introduction

Chiral amines are valuable building blocks in organic synthesis and key structural elements in numerous natural products, pharmaceuticals, and functional materials.¹⁻¹¹ As an important subclass of this family, chiral α -tertiary *N*-arylamines are prevalent in many bioactive compounds,¹²⁻¹⁶ and thus great effort has been devoted to their efficient synthesis (Scheme 1a). Among them, the asymmetric addition to ketimines¹⁷⁻²⁵ and the *N*-alkylation of arylamines with diverse electrophiles²⁶⁻³² represent the most prevalent methods for constructing chiral α -tertiary *N*-arylamine scaffolds (Scheme 1b). Given the importance of the structural motifs, there is a strong need for the development of new synthetic methods from readily available starting materials.

Alkenes are readily available feedstocks and serve as ideal starting materials for diverse transformations in organic synthesis. The asymmetric intermolecular 1,2difunctionalization of alkenes, enabling the simultaneous installation of two vicinal new bonds in one step, provides a powerful tool for transforming the alkene feedstocks into chiral complex molecules.³³⁻⁴³ On the other hand, the last decade has witnessed the renaissance of radical reactions, attributed to the gentle generation of radicals from diverse precursors under mild conditions.44-47 In this regard, the radical-mediated asymmetric three-component 1,2-difunctionalization of alkenes has spurred significant interest due to the high propensity of radicals toward the alkene moiety.48-56 In the well-established methodologies, the key chiral bond formation is typically achieved through the interaction of the nucleophile-sequestered chiral 3d transition metal with the prochiral alkyl radical derived from the radical alkene addition. Utilizing this strategy, we envisioned that the asymmetric radical 1,2-carboamination of 1,1-disubstituted alkenes with arylamines would provide expedient access to value-added chiral α -tertiary *N*-arylamines (Scheme 1c). However, despite the impressive progress in the racemic radical alkene carboamination with arylamines, the asymmetric transformation has been less recognized.57-63 In this context, Liu's group,⁶⁴ Feng's group,⁶⁵ and others^{66,67} have reported elegant approaches to achieve asymmetric radical 1,2-carboazidation of disubstituted alkenes. Although the protocol provided an array of chiral α tertiary azides, it took tedious synthesis to convert the azido group into the corresponding N-arylamine moiety. Therefore, the development of a new catalytic system to directly achieve the asymmetric radical 1,2-carboamination of 1,1-disubstituted alkenes with arylamines from readily available feedstocks is highly desirable.

As our continuous interest in developing asymmetric radical transformations,⁶⁸⁻⁷⁴ we have described an enantioconvergent C-N cross-coupling of alkyl halides with arylamines through the interaction of alkyl radicals with



Scheme 1 | *Asymmetric radical 1,2-carboamination of 1,1-disubstitued alkenes.*

ligand-chelated Cu(II) anilide complex.⁷⁵ We wondered whether an asymmetric three-component alkene 1,2-carboamination could be achieved by merging the C-N formation with the radical alkene addition process, utilizing readily available alkyl halides as radical precursors. However, we envisaged that the two-component C-N cross-coupling might impede three-component alkene 1,2-carboamination. Our initial attempts using the previously used α -carbonyl tertiary alkyl halides⁷⁶⁻⁷⁸ as radical precursors showed that the C-N cross-coupling could compete with the carboamination process (Supporting Information Scheme S1). Given that the cyano group was readily converted into carbonyl and amine moieties, we chose commercially available bromoacetonitrile as the radical precursor. It should be noted that the redox potential of bromoacetonitrile is relatively inert $[E_{1/2}^{\text{red}} = -0.69 \text{ V vs saturated calomel electrode (SCE)}$ in dimethylformamide (DMF)] and the reducing capability of copper salt is too weak to initiate the radical process.⁷⁹⁻⁸³ Based on our previous study, we surmised that the multidentate chiral anionic ligand could greatly enhance the reducing capability of copper catalyst for reaction initiation.⁶⁹ Hereby, we describe a copper-catalyzed asymmetric 1,2-carboamination of 1,1-disubstituted alkenes from readily available alkyl halides and arylamines, providing a variety of chiral α -tertiary N-arylamines. The key to the success lay in the utilization of an anionic chiral N,N,N-ligand, which greatly enhanced the reducing capability of copper catalyst for reaction

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initiation and achieved enantiocontrol over the sterically congested tertiary alkyl radicals. The reaction covered a wide range of arylamines, accommodating strongly coordinating heteroaryl amines, as well as 1,1-disubstituted acrylamides with good functional group tolerance. The scope of radical precursors was quite broad, encompassing not only primary alkyl bromides but also the pharmaceutically relevant trifluoromethyl group and the heteroatomic sulfonyl group. Further, straightforward manipulation of the carboamination products led to many other chiral α -tertiary *N*-arylamine scaffolds of interest in organic synthesis.

Results and Discussion

Reaction development

At the outset, we investigated the ligand effect for the three-component model reaction of alkene **1a**, arylamine **2a**, and bromoacetonitrile **3a** in the presence of Cul/Cs₂CO₃ in tetrahydrofuran (THF) (Table 1). The commonly used neutral bisoxazoline ligand **L*1** failed to

Table 1 | Effect of Ligands and Optimal Conditions on aModel Copper-Catalyzed Asymmetric Three-ComponentRadical Carboamination Reaction^a



^a Reaction conditions: **1a** (0.05 mmol), **2a** (0.05 mmol), **3a** (0.075 mmol), Cul (10 mol %), **L*** (15 mol %), and Cs_2CO_3 (3.0 equiv) in THF (1.0 mL) at 30 °C for 72 h under argon; yield of **4** was based on ¹H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as an internal standard; the ee value was determined by HPLC analysis. ^b **1a** (0.05 mmol), **2a** (0.10 mmol), and **3a** (0.10 mmol) in benzene (1.0 mL).

initiate the reaction and alkene 1a was completely recovered. We then investigated the performance of tridentate chiral anionic ligands, which greatly enhanced the reducing capability of a copper catalyst.⁶⁹ Unfortunately, the previously reported N,N,P-ligand^{70,84} L*2 and N,N,Nligand^{71,85,86} L*3 in our asymmetric cross-coupling reactions afforded a trace amount of desired product 4, though alkene **1a** was partially consumed. We speculated that the cinchona alkaloid skeleton might be too crowded to facilitate the construction of the fully-substituted carbon stereocenter. We then switched to the less sterically bulky N,N,N-ligand that performed well in the construction of a fully-substituted carbon stereocenter.⁷⁵ To our delight, the desired 1,2-carboamination product 4 was generated in 55% yield with 79% ee in the presence of oxazoline-derived N,N,N-ligand L*4. Further investigation into the substituent on the oxazoline skeleton revealed that ligand L*5, bearing a phenyl substituent, significantly improved both the reaction efficiency and enantioselectivity, delivering 4 in 78% yield with 90% ee. Control experiments in which either a methyl group was installed at the *ortho* position of quinoline nitrogen (L*7) or the coordinating nitrogen (L*8) was removed led to a trace amount of 4 and full recovery of alkene 1a, illustrating the substantial role of the coordinating guinoline nitrogen. Replacing L*5 with its enantiomer L*9 provided the desired product 4 in 80% yield with 90% ee. After further optimization of the reaction parameters, including the copper catalysts, solvents, and the molar ratio of the reactants (Supporting Information Tables S1-S4), we finally identified the optimal conditions as follows: 1a (1.0 equiv), 2a (2.0 equiv), 3a (2.0 equiv), Cul (10 mol %), L*9 (15 mol%), and Cs_2CO_3 (3.0 equiv) in benzene at 30 °C for 72 h. Under the optimal conditions, the desired product 4 was obtained in 95% yield with 94% ee (Table 1).

Scope of alkenes

With the optimized conditions in hand, we first evaluated the scope of alkenes (Table 2). A range of morpholinederived 1,1-disubstituted alkenes underwent carboamination smoothly to give the desired products with good yield and ee. Electron-donating, -neutral, or -withdrawing groups at the para, meta, and ortho positions of the phenyl ring were all compatible with the reaction conditions to afford 4-14 with 92-94% ee. The 1- or 2-naphthyl substituent was also amenable to the process, yielding 15 and 16 with a similar ee. Notably, the yield was lower for the sterically congested ortho-substituted aryl and 1-naphthyl substrates (8 and 15). Moreover, a number of medicinally relevant heteroaryl rings such as benzo[d] [1,3]dioxole (17), furan (18), benzofuran (19), thiophene (20), and benzothiophene (21) were all tolerated. With regard to the amidyl group of the alkene substrates, a gamut of tertiary amides incorporating piperidine (22),



Table 2 | Scope of Alkenes^a



[°] Reaction conditions: **1** (0.20 mmol), **2a** (0.40 mmol), **3a** (0.40 mmol), Cul (10 mol %), **L*9** (15 mol%), and Cs₂CO₃ (3.0 equiv) in benzene (4.0 mL) at 30 °C for 72 h under argon; the yields were isolated and the ee value was determined by HPLC analysis.

thiomorpholine (23), pyrrolidine (24), indoline (25), and dimethylamine (26) all worked well to provide the desired products in good yields with 92–95% ee. Furthermore, a substrate bearing the Weinreb amide moiety proved to be suitable for the reaction, resulting in 27, albeit with a moderate ee.

Scope of aromatic amines and radical precursors

Next, we investigated the scope of the aromatic amines in this new asymmetric carboamination reaction (Table 3). A variety of arylamines proceeded smoothly to give the desired products **28-40** in moderate to excellent yields with good ee. With regards to potentially reactive functional groups, many functionalities such as halogen (**28-30**), trifluoromethyl (**31-33**), cyano (**32** and **35**), nitro (**33**, **37-39**), ester (**36**), and sulfone (**40**) at the *para* or *meta* positions of the aryl rings were left unscathed under the standard conditions. Since *N*-heterocycles are key structural units in many drugs and biologically interesting

DOI: 10.31635/ccschem.024.202404389 Citation: CCS Chem. 2024, 6, 2652-2661 Link to VoR: https://doi.org/10.31635/ccschem.024.202404389 molecules, we were pleased to find that a gamut of strongly coordinating N-heterocycles, including quinoxaline (41), pyridine (42), pyrimidine (43 and 44), and pyrazine (45) were viable amine substrates, yielding the desired products with 87-94% ee. Unfortunately, aniline and p-toluidine only gave rise to the desired products 46 and **47** with low ee, while aliphatic amine failed to afford the desired product 48. The subsequent evaluation of radical precursors further showcased the reaction diversity. For example, primary benzyl bromides with either electron-donating, -neutral, or -withdrawing groups on the aryl ring were suitable for the reaction, providing 49-51 in moderate to good yields with excellent ee. Besides, 2-(bromomethyl)naphthalene was a viable substrate, giving rise to 52 in 68% yield with 94% ee. Considering the versatility of alkynes as synthons for various C(sp²/sp³)-based functionalities, we examined the performance of propargyl bromide. Our finding revealed that it served as a good radical precursor, leading to the formation of 53 in 63% yield with 94% ee. Subsequent investigation led us to identify that a tertiary alkyl bromide was also compatible with the reaction. Interestingly, a pyrrolidone analog 54 was obtained using BrCF₂CO₂Et as the radical precursor. Bulkier radical precursor $BrC(Me)(CO_2Me)_2$ yielded 55 in only moderate yield with 86% ee. Notably, the direct cross-coupling of alkyl halides with amines led to low yields of 50 and 55. Based on the above results, we inferred that less sterically crowded primary alkyl halides generally afforded the desired products with high yields and sterically crowded ones generally gave the products with low yields. In addition, we found that Togni reagent II⁸⁷ was suitable for the transformation to afford the pharmaceutically relevant CF₃-containing product 56 with good ee. The scope of radical precursors was not limited to carboncentered ones; sulfonyl chlorides were also applicable to this transformation, furnishing the alkene sulfonylamination products 57-60 in moderate to good yields with 87-96% ee. The absolute configuration of **57** was determined to be R by X-ray analysis (Supporting Information Figure S1) and those of other products were assigned by analogy. These results highlighted the extensive diversity within arylamines and radical precursors.

Synthetic utility

To show the preparative utility of the strategy, a gramscale reaction was carried out to afford the desired product **4** without a significant decrease in efficiency (Scheme 2a). The most important application was the provision of an opportunity to generate other valuable chiral α -tertiary *N*-arylamine building blocks. For example, the carboamination product **4** was easily converted into chiral 1,4-diamine **61** and γ -amino amide **62** through straightforward reduction or hydrolysis of the cyano group (Scheme 2b). Moreover, the carboamination



Table 3 | Scope of Arylamines and Radical Precursors^a

^a Reaction conditions: **1a** (0.20 mmol), **2** (0.40 mmol), **3** (0.40 mmol), Cul (10 mol %), **L*9** (15 mol %), and Cs₂CO₃ (3.0 equiv) in benzene (4.0 mL) at 30 °C for 72 h under argon; the yields were isolated and the ee value was determined by HPLC analysis.

product **49** was successfully transformed into α -amino aldehyde **63** via a simple reduction of the amide moiety. Further reduction of the aldehyde moiety of **63** led to chiral 1,2-amino alcohol **64** in good efficiency. To further showcase the synthetic potential, we performed a Wittig reaction of **63**, which afforded a carbon chain-elongated building block **65**. Notably, no apparent loss of enantiopurity was observed during all the transformations. Collectively, these results demonstrated the practicality of this methodology in synthesizing other α -tertiary *N*-arylamine building blocks.

Mechanistic studies

To gain insights into the reaction mechanism, a radical inhibiting experiment conducted with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) showed complete inhibition of the reaction, and the TEMPO-trapped product **66** was formed in 43% yield (Scheme 2c). This experiment indicated the generation of an alkyl radical from bromoacetonitrile. Further control experiments demonstrated that no product derived from radical addition to alkene was observed, and complete recovery of alkene **1a** was detected. This finding suggested that the ligand exchange of arylamine with the copper catalyst likely occurred before the single-electron reduction of the alkyl halide (Scheme 2c). In addition, the radical clock substrate **67** afforded the desired product **68** together with the corresponding radical cyclization product 69 under the typical conditions (Scheme 2d). This experiment provided strong support for the formation of the corresponding tertiary alkyl radical resulting from the process of radical addition to alkene. Based on these experiments and our previous reports,⁷⁵⁻⁷⁸ we proposed a plausible mechanism as depicted in Scheme 2e. First, the copper(I) salt reacted with ligand L* and base to generate a complex I. This complex underwent a subsequent ligand exchange with arylamines 2 to afford a nucleophile-sequestered copper(I) intermediate II, which reacted with radical precursors **3** to give an R radical and a copper(II) complex III via a single-electron reduction process. The R radical added to the terminal position of alkenes 1 and gave rise to a tertiary alkyl radical IV, which then interacted with complex III to deliver the desired carboamination products 4-60 and regenerated the copper(I) species I for the next catalytic cycle. In the case of





Scheme 2 | Synthetic utility and mechanistic discussion: Boc₂O, di-tert-butyl dicarbonate.

aromatic amines with electron-neutral or -donating groups, a direct nucleophilic attack on the carbocation species V by aromatic amines might have existed in the key C-N formation step, leading to dramatically decreased enantioselectivity (Scheme 2e).

Conclusion

We have developed a copper-catalyzed asymmetric radical 1,2-carboamination of 1,1-disubstituted alkenes from readily available alkyl halides and arylamines. The key to the reactions' success lay in the merger of radical addition to alkenes and chiral C-N formation process while suppressing the direct C-N coupling of alkyl halides with arylamines. The utilization of a chiral *N,N,N*-ligand was essential for initiating the reaction by enhancing the reducing capability of copper and enabling enantiocontrol over sterically congested tertiary alkyl radicals. One striking feature of this strategy was the effective accommodation of readily available acrylamides, aryl- and heteroaryl amines, as well as alkyl halides and sulfonyl chlorides, permitting good functional group tolerance. This strategy provides expedient access to a range of chiral α -tertiary *N*-arylamine building blocks of interest in organic synthesis.

Supporting Information

Supporting Information is available and includes details on reaction optimizations, experimental procedures, synthetic utility, mechanistic studies, and compound characterization data. All data supporting the findings of this study are available within the article and its Supporting Information. The supplementary crystallographic data for this paper was deposited at the Cambridge Crystallographic Data Centre (CCDC 2348262).

Author Contributions

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J.-H. Fang, J.-J. Chen, X.-Y. Du, and Z. Dong contributed equally to this research study. The manuscript was

prepared by contributions from Prof. Dr. X.-Y. Liu and Dr. Z.-L. Li.

Conflict of Interest

The authors declare no competing interests.

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