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Enantioenriched α-Quaternary α-Amino Amides via Copper-Catalyzed Propargylic Amination

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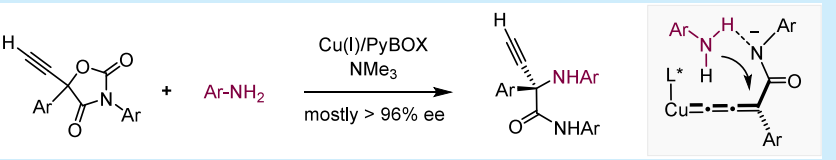
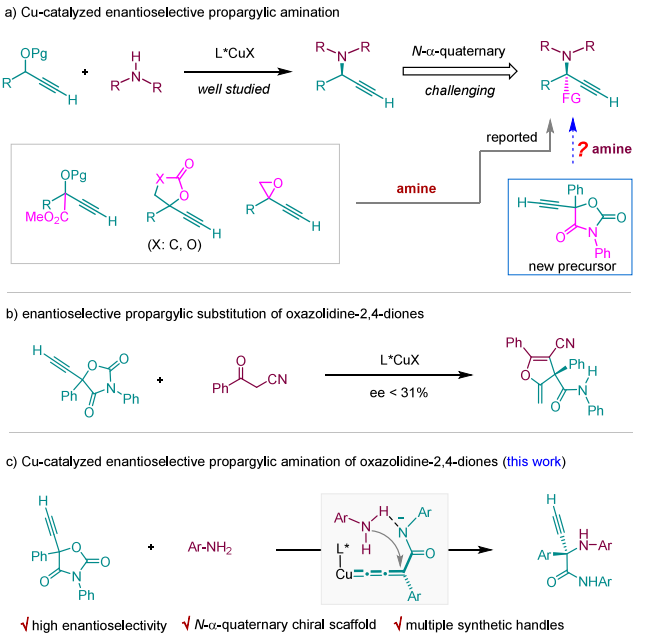


ABSTRACT: Catalytic enantioselective propargylic amination represents a valuable method toward the synthesis of functionalized amines. Current methods are mostly restricted to the use of sterically unhindered propargylic esters, thus yielding *N*-α-secondary chiral amines. Reported herein is a copper-catalyzed asymmetric propargylic amination of oxazolidine-2,4-diones, enabling efficient access to enantioenriched α-quaternary amides bearing terminal alkyne and amino groups. The mild conditions are amenable to a broad range of oxazolidine-2,4-diones and aryl amines in good yields with high enantioselectivity.

Enantioenriched propargylamines represent privileged structural motifs that serve as versatile building blocks for the rapid assembly of complex molecules, with applications spanning from organic synthesis[1−6] to drug discovery.[7−11] Over the past few decades, their broad utility has called for development of various methods for the preparation of chiral functionalized propargyl.[12−16] Of the many strategies of chiral propargylamine synthesis,[17−38] copper-catalyzed asymmetric propargylic amination has become a particularly attractive strategy. This method leverages electrophilic copper-allenylidene intermediates than deliver enantioenriched propargylamines with multiple advantages: (1) cost-effective and low-toxicity copper catalysts, (2) mild reaction conditions, (3) broad substrate tolerance, and (4) high enantioselectivity.[16] Since the pioneered asymmetric propargylic amination developed by van Maarseveen[18] and Nishibayashi,[19] copper-catalyzed asymmetric propargylic amination of propargylic esters using readily available aryl and alkyl amines has been extensively studied for the preparation of various secondary enantioenriched propargylic amines (Scheme 1a).[20−23,26,31,33] In addition to *N*-α-secondary propargylic amines, the employment of readilyu available α-ethynyl epoxides,[20,36] lactones,[26] cyclic carbonates,[27,30,35] and acyclic acetates[18,19,21,23,24,29,33,34] as propargylic precursors further made this propargylic amination strategy very attractive for accessing more challenging chiral *N*-α-quaternary propargylamines bearing synthetically useful hydroxy, carboxylic acid, and carboxylate groups. Most recently, the Zhou group developed an asymmetric copper-catalyzed propargylic amination of simple ketone-derived propargylic carbonates to give α-quaternary propargyl amines as well as azacycles via metal-catalyzed sequential cyclization.[39] Despite these enlightening advances, the novel substrate scaffold still awaits exploration to furnish

Scheme 1. Catalytic Propargylic Substitution



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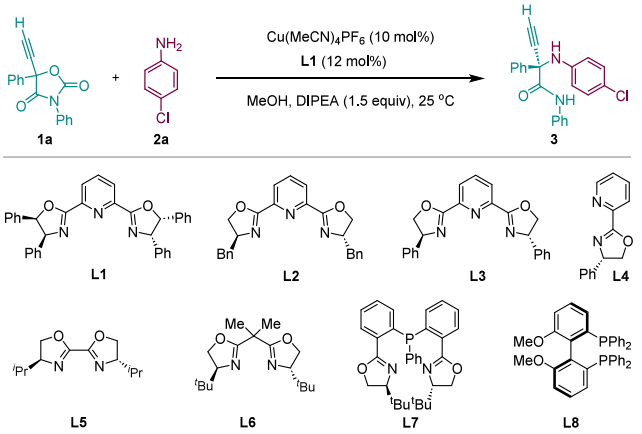
compounds bearing structurally diverse functional groups. For instance, the synthesis of enantioenriched α-quaternary α-amino amides via this methodology remains underdeveloped. This challenge in methodologic development underscores the continued need for innovative substrate design in propargylic amination reactions to enrich the arsenal of chiral functionalized amine synthesis.

Besides acyclic terminal propargylic acetates, cyclic propargyl carbonates/carbamates such as ethynyl ethylene carbonate[30,40−42] and ethynyl indoloxazolidone,[43,44] among others,[45−53] have also been widely used as versatile electrophilic copper-allenylidene precursors through a CO_2 extrusion process, delivering a range of enantioenriched functionalized cyclic scaffolds. However, as an important cyclic propargylic precursor, 5-ethynyloxazolidine-2,4-dione remained unexplored for such enantioselective transformations, although the Guo group reported a copper-catalyzed asymmetric [3 + 2] annulation with benzoylacetonitriles to afford 2,3-dihydrofuran derivatives with low enantioselectivity (<31% ee, Scheme 1b).[54] We hypothesized that 5-ethynyloxazolidine-2,4-diones could generate reactive copper-allenylidene intermediates bearing an amide moiety upon decarboxylation. Crucially, the resulting amide moiety could engage in hydrogen-bonding interactions with an incoming amine, potentially enabling highly enantioselective transformations. Building on this concept, we now report our findings on the copper-catalyzed asymmetric propargylic amination of 5-ethynyloxazolidine-2,4-diones with anilines, affording α-quaternary α-amino amides with excellent enantioselectivity (Scheme 1c).

Our investigation commenced with a model reaction between oxazolidine-2,4-dione **1a** and an aryl amine **2a** (Table 1). Initial screening revealed that the combination of $Cu(MeCN)_4PF_6$ and chiral pyridinebisoxazoline (PyBox) ligand **L1** gave the desired propargylic amine **3** in 65% yield and 51% ee when the reaction was conducted in MeOH with DIPEA as a base at 25 °C for 12 h (entry 1). Systematic evaluation of PyBox ligands demonstrated that both the bisoxazoline scaffold and the phenyl substituent on the oxazoline ring are crucial for the enantioselectivity control (entries 2−4). Subsequent screenings were conducted using other commercially available chiral ligands, including bisoxazolines (**L5** and **L6**), bisoxazolinephosphine (**L7**), and diphosphine (**L8**). Unfortunately, no improved enantioselectivity was realized using these chiral ligands (entries 5−8). Solvent optimization studies identified THF as the optimal media, providing both improved yield and enantioselectivity (entries 9−13). Further examination of bases showed that trimethylamine (Me_3N) significantly enhanced the stereoselectivity to 95% ee (entry 15). Finally, the stereoselectivity was further improved to 98% when the reaction was performed at a temperature of 20 °C (entry 16).

Having established the optimal conditions, we embarked on investigating the generality of this propargylic amination (Scheme 2). We first evaluated the scope with respect to the arylamines. The enantioselective propargylic aminations accommodated an array of substituents on the phenyl rings, including both halogen (chloro, fluoro, bromo, and iodo) and electron-donating (methyl and methoxy) groups at the *para*, *meta*, and *ortho* positions, affording the corresponding α-quaternary α-amino amide products **3**−**13** in yields ranging from 43% to 98% and up to 98% ee. The absolute configuration of **6** was determined by X-ray crystallography (CCDC 2409171). Of note, substituents such as *p*-bromo (**6**)

Table 1. Optimization Studies[a]



Entry	Variation from conditions	Yield, %[b] (ee, %)[c]
1	none	65 (51)
2	**L2**	60 (9)
3	**L3**	65 (50)
4	**L4**	35 (7)
5	**L5**	40 (3)
6	**L6**	51 (15)
7	**L7**	25 (<5)
8	**L8**	<5 (−)
9	**L1**, DCM	77 (65)
10	**L1**, PhMe	69 (71)
11	**L1**, MTBE	75 (70)
12	**L1**, 1,4-dioxane	59 (79)
13	**L1**, THF	79 (83)
14	**L1**, THF, TEA	80 (78)
15	**L1**, THF, Me_3N	81 (95)
16	**L1**, THF, Me_3N, 20 °C	85 (98)

[a]Reaction conditions: 5-ethynyl-3,5-diphenyloxazolidine-2,4-dione **1a** (0.1 mmol), 4-chloroaniline **2a** (0.12 mmol), $Cu(MeCN)_4PF_6$ (10 mol %), chiral ligand (12 mol %), and base (0.15 mmol) in solvent (1 mL) under N_2 for 12 h. [b]Isolated yield. [c]ee determined by HPLC analysis on a chiral stationary phase.

and *p*-iodo (**7**) groups were compatible with the catalytic system, giving the corresponding products valuable handles for further synthetic transformations. Disubstituted arylamines, including naphthalene and 3-chloro-4-morpholinobezene, were also investigated, leading to the corresponding products (**14** and **15**) in good yields with outstanding enantioselectivities. Additionally, the phenyl ring equipped with phenylethynyl and ethynyl groups at the *para* position tolerated the reaction well, affording the diethynyne-substituted products (**16** and **17**, respectively) efficiently. However, aliphatic amines failed to give any corresponding product under the current reaction conditions.

After the establishment of the optimal reaction conditions, we next explored the scope of 5-ethynyloxazolidine-2,4-diones with 4-chloroaniline as the model nucleophile. The catalytic system exhibited remarkable tolerance toward diverse *N*-aryl substituents on the oxazolidinedione scaffold. A series of *para*-halogenated (F, Cl, Br, and I) aryl groups, as well as those bearing strong electron-withdrawing trifluoromethyl and trifluoromethoxy substituents, all participated effectively in the transformation, furnishing the corresponding propargylic amines (**18**−**23**) with excellent enantioselectivities (98% ee). Installation of electron-rich phenyl rings such as *p*-methyl-

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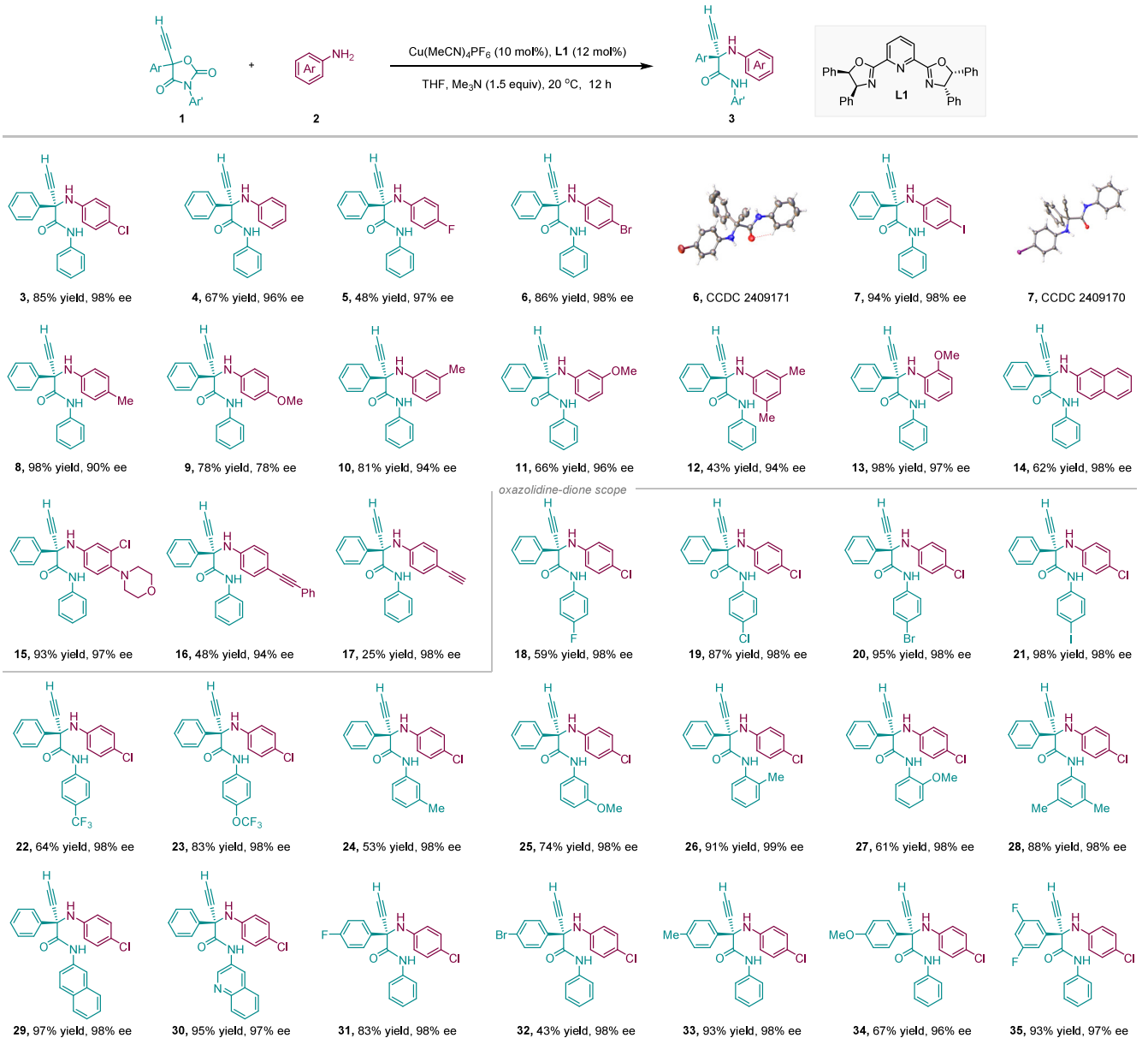
Scheme 2. Substrate Scope[a]



[a]Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), $Cu(MeCN)_4PF_6$ (10 mol %), **L1** (12 mol %), and Me_3N (75 μL, 2 M in THF) in THF (1 mL) at 20 °C under N_2 for 12 h. Isolated yield. The ee was determined by HPLC analysis on a chiral stationary phase.

phenyl, *m*-methoxyphenyl, *o*-methylphenyl, and 3,5-dimethylphenyl substituents to the nitrogen atom was also tolerated. These substrates afforded the desired products (**24**–**28**) in 53–91% yields with excellent enantioselectivities. Notably, extended π-systems such as naphthyl and quinoline derivatives (**29** and **30**) also worked well under the optimized conditions. Finally, the influence of the propargylic aryl groups was evaluated. We found that electron-rich and electron-deficient aryl substitutions at the *para* and *meta* positions yielded good to excellent results with high levels of enantioselectivity (**31**-**35**).

A large-scale synthesis of chiral propargylic amine **3** was performed without a loss of yield or enantioselectivity (Scheme 3). To further substantiate the synthetic utility of this propargylic amination system, a series of derivatization experiments were carried out to exploit the multiple potential modification sites of the products. Palladium-catalyzed semihydrogenation of the alkynyl moiety gave allylic amine **36** in 78% yield with 99% ee. The terminal alkyne of product **3** was readily transformed to an internal alkyne (**37**) in high yield with high enantioselectivity via Sonogashira coupling. In addition, copper-catalyzed cycloaddition between an azide and product **3** afforded triazole **38**.

To investigate the mode of substrate activation, we first examined an oxazolidine-2,4-dione bearing an internal alkyne as the substrate. However, no desired product was observed (Scheme 4, top). When a perdeuterated aniline was employed, propargylic amination proceeded to furnish the corresponding product with 49% deuterium incorporation at the terminal alkynyl position. These experimental results suggest that the oxazolidine-2,4-dione activation likely proceeds through an alkynylcopper intermediate that undergoes further protonol-

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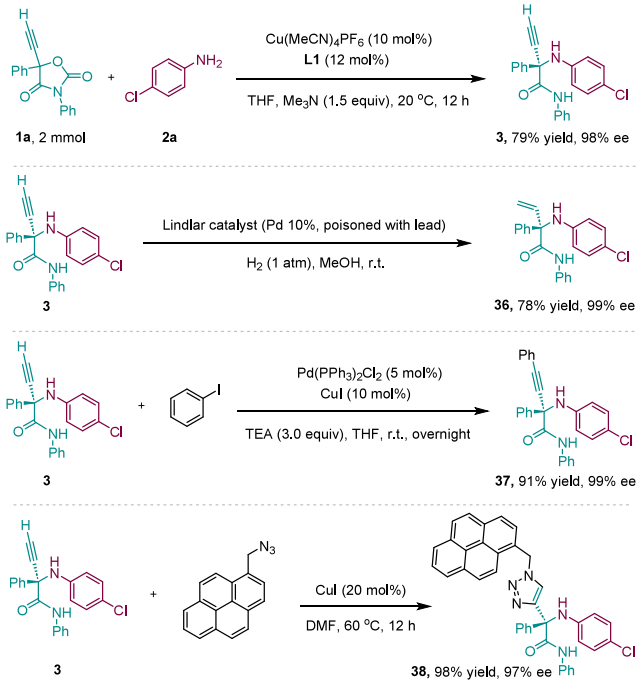
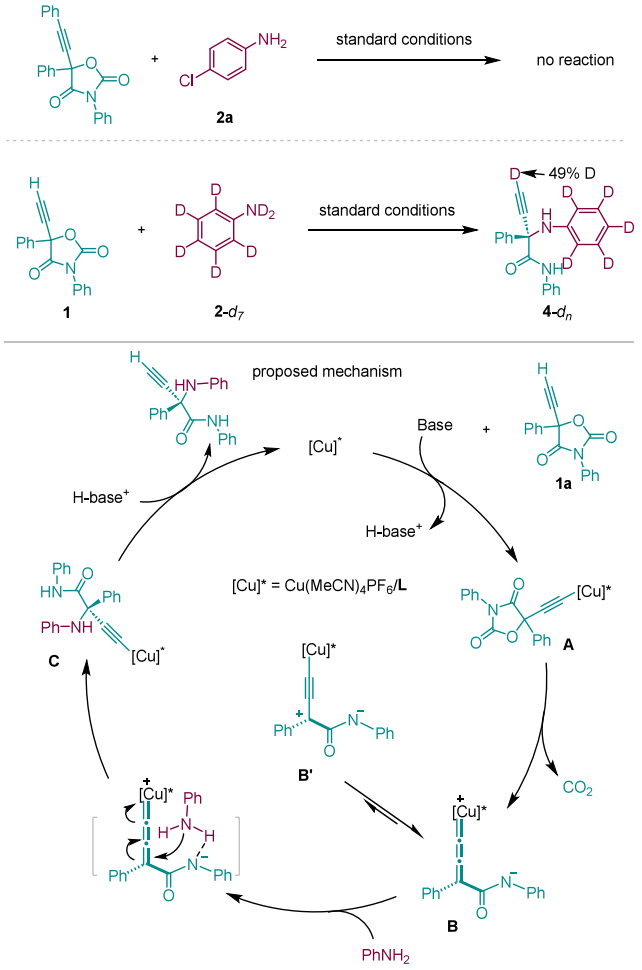
Scheme 3. Product Transformations



Scheme 4. Mechanistic Studies and Proposed Catalytic Cycle



ysis. Based on these preliminary experimental results and previous work,[21,55] we proposed a mechanism as depicted in Scheme 4 (bottom). Initial base-assisted deprotonation of the terminal alkyne generates alkynylcopper intermediate **A**, which undergoes ring opening of oxazolidinedione upon decarboxylation to give electrophilic copper allenylidene species **B**. Enantioselective nucleophilic addition of an aniline yields an alkynyl copper intermediate **C**. Finally, protonation of the copper acetylide species furnishes the desired chiral product and regenerates the copper(I) catalyst.

In summary, we have developed a copper-catalyzed enantioselective propargylic amination of oxazolidine-2,4-diones. This method exhibits a broad substrate scope in terms of arylamines and oxazolidinediones, high functional-group tolerance, and excellent enantioselectivity, allowing straightforward access to structurally diverse *N*-*α*-quaternary chiral amines bearing terminal alkyne and amide groups as post-transform handles for further derivatization. Given the synthetic flexibility of these scaffolds, significant utility is anticipated for rapid assembly of highly functionalized structures.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c02307.

Experimental details, characterization of all new compounds, the X-ray crystal structure, and NMR spectra (PDF)

Accession Codes

Deposition Numbers 2409170−2409171 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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